Official Title:
A Study in Adults on Pre-LT Dialysis With Basiliximab, Delayed Tacrolimus (TAC), Mycophenolate (MMF), and Steroids (Group 1) vs. Basiliximab, Delayed TAC, MMF, Steroids, With Everolimus 30 Days Post-LT (Group 2) vs. TAC, MMF, and Steroids (Group 3)

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Study Synopsis

TITLE

An single center, open label, randomized, prospective, phase 4 study of induction and maintenance immunosuppression in adult subjects age >18 years undergoing orthotopic liver transplantation (OLT) with basiliximab, delayed dose tacrolimus plus mycophenolate mofetil and standard of care (SOC) corticosteroids (Group 1) versus basiliximab, delayed dose tacrolimus plus mycophenolate mofetil, SOC corticosteroids, with addition of delayed maintenance everolimus at one month post OLT with subsequent mycophenolate mofetil minimization (Group 2) versus standard dose tacrolimus plus mycophenolate mofetil plus SOC corticosteroids (Group 3; control) with a high risk of developing renal dysfunction following OLT or with concomitant renal dysfunction prior to OLT.

OBJECTIVES

To assess the efficacy and safety of basiliximab, delayed dose tacrolimus plus mycophenolate mofetil, and SOC corticosteroids versus basiliximab, delayed dose tacrolimus plus mycophenolate mofetil, and SOC corticosteroids and addition of delayed everolimus/mycophenolate minimization at one month post OLT compared to standard triple immunosuppression (tacrolimus, mycophenolate mofetil and corticosteroids) for prevention of acute organ rejection in liver transplant recipients with a high risk of developing renal dysfunction following OLT or with concomitant renal dysfunction prior to OLT.

STUDY DESIGN: single center, randomized, prospective, pilot

DRUG THERAPY

Group 1

Basiliximab

- Dose #1: 20mg IV within 2 hours of transplant
- Dose #2: 20mg IV Post-operative day #4

Tacrolimus (with basiliximab induction)

- Beginning day #5 post-transplant or when SCr ≤ 1.8 mg/dl (subjects off dialysis) to six months: 0.03-0.1mg/kg q12h PO to maintain whole blood trough concentration of 4-6ng/mL

Mycophenolate mofetil

- 500 mg po bid

Corticosteroids (SOC): Per UCLA protocol

Post-operative taper:

- Post-op day 1- methylprednisolone 50mg IVP Q6H
- Post-op day 2- methylprednisolone 40mg IVP Q6H
- Post-op day 3- methylprednisolone 30mg IVP Q6H
- Post-op day 4- methylprednisolone 20mg IVP Q6H
- Post-op day 5- methylprednisolone 20mg IVP Q12H
- Post-op day 6- methylprednisolone 10mg IVP Q12H
  until taking PO, then change to: prednisone 20mg PO QAM

Group 2

Basiliximab

- Dose #1: 20mg IV within 2 hours of transplant
- Dose #2: 20mg IV Post-operative day #4

Tacrolimus (with basiliximab induction)

- Beginning day #5 post-transplant or when SCr ≤ 1.8 mg/dl (subjects off dialysis) to POD 30: 0.03-0.1mg/kg q12h PO to maintain whole blood trough concentration of 4-6ng/mL
- POD 31; reduce to tacrolimus to 2-5ng/mL in presence of everolimus levels 3-8 ng/mL

Mycophenolate mofetil

- 500 mg po bid up to POD 30: reduce mycophenolate mofetil following achievement of steady state everolimus (POD 35) as clinically indicated

Corticosteroids (SOC): Per UCLA protocol

Post-operative taper:

- Post-op day 1- methylprednisolone 50mg IVP Q6H
- Post-op day 2- methylprednisolone 40mg IVP Q6H
- Post-op day 3- methylprednisolone 30mg IVP Q6H
- Post-op day 4- methylprednisolone 20mg IVP Q6H
- Post-op day 5- methylprednisolone 20mg IVP Q12H
- Post-op day 6- methylprednisolone 10mg IVP Q12H
  until taking PO, then change to: prednisone 20mg PO QAM

Everolimus (delayed)

- Add by POD 30: 1 mg po bid and adjusted to maintain whole blood trough concentrations of 3-8 ng/ml.

Group 3 (control):

Tacrolimus (without basiliximab induction)

- Beginning day #1 post-transplant to six months: 0.03-0.1mg/kg q12h po to maintain whole blood trough concentration of 5-12ng/mL
- Six months to one year: maintain whole blood trough concentration of 5-10ng/mL

Mycophenolate mofetil

- 500 mg po bid

Corticosteroids (SOC): Per UCLA protocol

Post-operative taper:

- Post-op day 1- methylprednisolone 50mg IVP Q6H
- Post-op day 2- methylprednisolone 40mg IVP Q6H
- Post-op day 3- methylprednisolone 30mg IVP Q6H
- Post-op day 4- methylprednisolone 20mg IVP Q6H
- Post-op day 5- methylprednisolone 20mg IVP Q12H
- Post-op day 6- methylprednisolone 10mg IVP Q12H
  until taking PO, then change to: prednisone 20mg PO QAM

PATIENT POPULATION

In a 2:2:1 fashion, 90 subjects (group 1: n=36; group 2: n=36; group 3: n=18) will be randomized at UCLA Medical Center. Each subject will be followed for 6 months post-transplant.

PRIMARY ENDPOINTS

- Assessment of the nephroprotective effects of everolimus in combination with simulect, or simulect alone following OLT at months 2, 3, 4, 5 and 6.

SECONDARY ENDPOINTS

- Mean serum creatinine, eGFR (MDRD) at weeks 1, 2, 4, 8, 12, 16, 20 and 24
- 1, 3 month and 6 month cumulative incidence of acute allograft rejection episodes, steroid resistant rejection episodes, dialysis requirements
- Incidence of death and/or graft failure at 6 months
- Tolerability and side effect profile of the combination drug therapies
- Incidence of infectious complications
- Time to first episode of acute rejection
- Refractory rejection episodes (requiring immunosuppression beyond T cell depletion)
- Rejection episodes per subjects
- Number of subjects requiring full-dose calcineurin inhibitor rescue therapy
- Monitor CD_{25} cell count for 3 months
- Economic analysis to determine cost-effectiveness of induction therapy with IL-2 monoclonal antibody
- Economic analysis to determine cost-effectiveness of delayed therapy with mTOR

A three arm, single center, randomized, prospective, pilot trial of induction and maintenance immunosuppression with basiliximab, delayed dose tacrolimus plus mycophenolate mofetil, and SOC corticosteroids versus immunosuppression with basiliximab, delayed dose tacrolimus plus mycophenolate mofetil, and SOC corticosteroids with delayed addition of everolimus and mycophenolate minimization versus standard dose tacrolimus and mycophenolate mofetil plus corticosteroids in patients undergoing orthotopic liver transplantation (OLT) with concomitant renal dysfunction

Introduction (Background and Rationale)

Renal disease is commonly found in patients undergoing liver transplant evaluation. In the terminal stages of liver disease, approximately 75% of patients develop oligoanuric renal failure. [1] One study of 102 liver allograft recipients revealed 25% experienced renal impairment before transplantation and 67% after transplantation.[2] This study also showed that pre-transplantation renal dysfunction was an independent predictor of postoperative mortality. Numerous factors may affect renal function in the end-stage liver disease patient. Some include hepatorenal syndrome, the complexity of the operation for liver transplantation, and the potential for postoperative graft dysfunction. [3,4] Furthermore, the incidence of short term renal dysfunction can be linked to the pre-transplant model for end stage liver disease (MELD) score. Specifically, elevations in pre-transplant serum creatinine which is one of three factors used to calculate the MELD score for organ allocation are associated with reduction in renal function and are a negative predictive factor for patients with cirrhosis (and after OLT). [4]

Despite extensive knowledge of post operative renal dysfunction in liver transplant recipients, chronic renal failure following liver transplantation remains one of the most challenging complications with chronic renal failure occurring in up to 18-20% of OLT recipients after five years [5,6]. The etiology of altered renal function following OLT is complex, but one of the most important risk factors is the nephrotoxic effects of the therapeutic agents required to guard against rejection, namely long term calcineurin inhibitor usage. [1,7] Tacrolimus (TAC) and cyclosporin (CYA), are known as the calcineurin inhibitors (CNIs). These immunosuppressive drugs are routinely used to help prevent rejection following solid organ transplantation. Along with other advances, these agents have helped most liver transplant centers achieve one year survival rates higher than 85% because of better clinical management.[8] Nephrotoxicity is the most notable adverse effect associated with CNI therapy. CNIs can cause long-term structural and functional changes to the kidney, contributing to the long term problems seen in transplant patients. [9-11] Histologically, striped tubulointerstitial fibrosis, tubular atrophy, and afferent arteriolopathy are noted. [9,12-14] CNIs have been reported to elucidate transient reductions in renal plasma flow and glomerular filtration rate that results from acute, reversible renal hypoperfusion with the greatest change in GFR in the first 3-6 months. [15] This continual renal hypoperfusion might explain the structural changes and long term functional deterioration of the pre-glomerular, afferent arterioles and be a critical indicator of future problems.

Therefore, OLT recipients with pre-existing renal impairment or high (renal driven) MELD scores could benefit from alternative immunosuppressive strategies in the immediate and long term post-transplant settings. Immunosuppressive regimens that are calcineurin

sparing, calcineurin free or regimens that add novel agents such as mTOR inhibitors (e.g. everolimus) at specific times following transplant in order to reduce CNI exposure or withdraw them entirely have been suggested and studied on a limited basis. [16-20]

Recently at our center, we completed a pilot trial in 60 adult OLT recipients in which we compared our standard triple immunosuppressive therapy with TAC plus myfortic and a standard of care corticosteroid taper to induction therapy with basiliximab with delayed use of tacrolimus therapy (until post-operative day 7), combined with myfortic and a rapid corticosteroid taper. The delay in tacrolimus therapy in the basiliximab induction group resulted in a mild improvement in renal function by three months following transplant while maintaining adequate immunosuppression to prevent acute rejection. This study was limited in the number of subjects enrolled and suffered from an inability to further reduce CNI exposure and perhaps enhance renal recovery or improvement following OLT. Thus additional CNI sparing agents could benefit these recipient with respect to enhancing renal function over time.

Everolimus is an mTOR inhibitor that is a structural derivative of sirolimus, with a distinct pharmacokinetic profile (shorter half-life and twice a day dosing). Clinical experience showed that a pharmacokinetic interaction of tacrolimus on everolimus may be less than with cyclosporine or even absent, and that the combination of everolimus and tacrolimus was safe and well tolerated with no new safety risks identified. [21, 22]

It has been approved for use in liver transplant recipients in combination with corticosteroids and reduced dose tacrolimus. Approval was based on a large study (n=719) in which delayed everolimus (introduced POD 30) with reduced dose tacrolimus (39% reduction of tacrolimus) showed comparable efficacy (incidence of biopsy proven acute rejection, graft loss or death) and had superior renal function as early as 1 month compared to standard dose tacrolimus. [23] Additionally, several small or retrospective studies have reported the use of everolimus in OLT recipients in combination with CNI reduction or as a CNI withdrawal strategy. [24-26]

Similar to the CNIs, everolimus administration includes trough level therapeutic drug monitoring (TDM). This practice has evolved largely due to the relatively narrow therapeutic window for immunosuppression, the considerable inter- and intraindividual pharmacokinetic variability, as well as the high incidence of drug-drug interactions resulting from hepatic metabolism via cytochrome P450 isoenzyme 3A4 (CYP3A4). Results in adults using therapeutic drug level monitoring of everolimus target an everolimus C-0h blood trough level of 3-8 ng/mL. [27, 28]

Previously, the risk of hepatic artery thrombosis (HAT), leading to an increased rate of patient death within the first 30 days post-transplantation, was identified as a concern after liver transplantation using sirolimus. [29] However, recent results suggest that sirolimus used at low doses or early after the immediate peri-operative period was not associated with HAT. [30] HAT has neither been associated with the use of everolimus. [31] However, the Phase III trial conducted in *de novo* adult whole liver transplantation implemented delayed everolimus administration (POD 30 ± 5 days) to limit the risk of drug induced HAT.

Therefore, based on the available data and experience in OLT recipients and building on our previous UCLA pilot trial design and experience, the potential benefit from the introduction of delayed everolimus and improved renal function related to reduction of calcineurin inhibitors (CNI) over time and enhanced safety profile warrants additional investigation.

Thus, we propose a randomized, prospective investigator initiated study that will compare basiliximab induction, delayed TAC exposure plus MMF and a SOC corticosteroid taper (group 1; n=36), compared to basiliximab induction, delayed TAC exposure plus MMF and a SOC corticosteroid taper with a delayed everolimus facilitated CNI reduction at POD 30 and mycophenolate minimization to further enhance renal function (group 2; n=36) versus control (standard dose TAC plus MMF and standard of care corticosteroid taper; group 3; n=18).

Clearly, the primary objective assesses rate and severity of rejection, allograft loss and death as well as post-operative renal function (measured as estimated GFR). The proposed study will also evaluate the mTOR class effects (e.g., dyslipidemia, impaired wound healing and proteinuria) and in addition, it will monitor closely the potential safety effects of chronic mTOR inhibitor therapy upon infectious complications such as CMV, and HBV and HCV.

Purpose

Primary Objectives

- To evaluate the evolution of renal function assessed by dialysis independence and time to independence from dialysis.

Secondary Objectives

- Glomerular Filtration Rate (eGFR); Cockcroft and Gault (MDRD)
- To determine the incidence of confirmed acute rejection episodes in patients undergoing orthotopic liver transplant at 1, 3 and 6 months post-transplant
- To determine the tolerability and adverse event profile of basiliximab, delayed dose tacrolimus, mycophenolate mofetil, SOC corticosteroids and Everolimus during the first six months post-transplant
- To determine the incidence of infectious complications during the first six months post-transplant
- To determine the time to the first episode of acute rejection
- To determine the severity of each acute rejection episode
- To determine the incidence of death and/or graft failure within the first six months post-transplant
- To determine the number of patients requiring full dose CNI rescue therapy
- To determine the mean serum creatinine concentration and eGFR: Cockcroft and Gault (MDRD) at weeks 1, 2, 4, 8, 12, 16, 20 and 24 post OLT
- To monitor CD_{25} cell count for the first 3 months post-transplant
- Economic analysis to determine cost-effectiveness of induction therapy with IL-2 monoclonal antibody
- Economic analysis to determine cost-effectiveness of delayed therapy with everolimus

Efficacy objectives at 1, 2, 3, and 5 months after start of everolimus

To assess:

- Rate of composite efficacy failure of treated biopsy proven acute rejection (tBPAR), graft loss (GL) or death (D).
- Time to event and severity of tBPAR.
- Incidence and severity of all acute rejection.

To evaluate:

- Renal function over time assessed by mean change in eGFR by the Cockcroft and Gault (MDRD) from the start of everolimus.
- Urinary protein/creatinine ratio at various time points
- Incidence of and time to renal replacement therapy.

Safety objectives

To evaluate:

- All AE/SAEs with emphasis on viral infections and reactivation (CMV, EBV, HIV, Hepatitis B and Hepatitis C), hematological and metabolic laboratory parameters, gastrointestinal side effects and malignancies.
- Incidence of treatment-related side effects including incidence of new onset diabetes mellitus (NODM), serum/blood lipid panel, neurotoxicity and hypertension.
- Incidence and reason (e.g. AE) for premature discontinuation of study medication, and premature withdrawal from the study.
- Incidence and reason (e.g. AE) for dose interruption and dose adjustment of study medication.

Rationale of dose/regimen, duration of treatment

The immunosuppressant drugs, basiliximab, tacrolimus, mycophenolate mofetil, corticosteroids (methylprednisolone/prednisone), and everolimus are marketed drugs and their dosage and administration will be based on label recommendations and clinical standards of care

Study Population

The study population will consist of adult (age >18 years) male and female primary liver transplant recipients. All patients will have received a liver allograft from a deceased donor.

It is anticipated our center will need to screen approximately 140 male and female adult liver transplant recipients. Of these 140 liver allograft recipients, it is expected a minimum of 90 will fulfill the inclusion and none of the exclusion criteria at baseline and will be able to be randomized in a 2:2:1 manner to receive one of the three proposed immunosuppressive regimens.

Inclusion Criteria at Baseline

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

1. A signed informed consent prior to patient participation in the study and before any assessment is performed.
2. Patients who are able to take oral medication at 1 month post transplant

3. ≥ 18 years old
4. Undergoing first OLT
5. Dialysis for 45 days or less at time of transplant
6. Able and willing to conform to requirements of the study
7. Able and willing to provide informed consent or have legally authorized representative who is able and willing to provide informed consent

Exclusion Criteria

1. < 18 years old
2. Autoimmune liver disease, Primary Sclerosing Cholangitis, Primary Biliary Cirrhosis
3. Dialysis greater than 45 days
4. Receiving ATG, IVIG therapy, or sirolimus/everolimus around time of transplant or sirolimus/everolimus after transplant
5. Unable to take oral medications at 1 month post transplant
6. Participating in another clinical research study involving the evaluation of another investigational drug or device
7. Documented allergy to basiliximab, TAC, MMF or any macrolide antibiotic.
8. Presence of thrombosis of any major hepatic arteries
9. Complex/high risk arterial reconstruction at any time (graft vessel patency by Doppler ultrasound confirmed and documented).
10. Patients who are recipients of multiple solid organ transplants, (e.g., multivisceral or combined liver-kidney transplants), or have previously received an organ or tissue transplanted, or who received an ABO incompatible transplant.
11. Patients who have severe hypercholesterolemia (>215 mg/dL; >5.5 mmol/L) or hypertriglyceridemia (>265 mg/dL; >3.0 mmol/L) at Baseline.
12. Patients who have severe thrombocytopenia or neutropenia (platelet count >20 and MLCs>1000)
13. Patients who have any surgical or medical condition, which in the opinion of the investigator, might significantly alter the absorption, distribution, metabolism and excretion of study drugs
14. Patients with a known hypersensitivity to the drugs used on study or their class, or to any of the excipients.
15. Patients with clinically significant systemic infection
16. Pregnant or nursing (lactating) female patients, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive βHCG laboratory test (>9 mIU/mL) at Baseline.

Investigational Treatment

Introduction and maintenance of everolimus

Everolimus will be introduced at the earliest 1 month after liver transplantation for all patients to minimize the potential risks of wound healing and vascular complications of the graft. At the start of the treatment period (Day 1), patients will receive the first dose of everolimus (1 mg twice daily in 12 hr intervals)

By Day 4, the everolimus dose will be adjusted to achieve targeted C-0h blood trough level between 3-8 ng/mL. All patients will continue to receive everolimus with CNI reduced dose for 6 months. Mycophenolate will be minimized as clinically indicated in subjects (group 2) receiving everolimus and tacrolimus.

The dose of everolimus must be taken twice-daily, 12 hours apart, in the morning and evening dose AFTER tacrolimus administration (everolimus or tacrolimus dose administrations should not be more than 10 minutes apart). The morning or evening everolimus dose should be taken consistently either with or without food as the patient prefers. To prevent alteration of study drug absorption, grapefruit or grapefruit juice are not allowed throughout the study.

Permitted dose adjustments and interruptions of study treatment

For patients who are unable to tolerate the protocol-specified dosing scheme, dose

adjustments and interruptions are permitted to allow the patient to continue on study drug. In general, in a first attempt to treat patients who have difficulties to tolerate their

immunosuppressive regimen, symptomatic treatment should be considered. The following guidelines should be followed.

Everolimus

The recommended route of administration for everolimus is orally, therefore patients who are unable to take oral medications by 1 month post transplant will be excluded from the study.

For patients for patients who are unable to tolerate the protocol-specified dosing scheme due to a decrease in the platelet count, a decrease in hemoglobin level, a decrease in white blood count, an increase in cholesterol level, an increase in triglyceride level, or

other adverse events, dose adjustments are permitted in order to keep the patient on the study drug.

The everolimus dose should be decreased by at least one third of the total daily dose of the study if a dose reduction is necessary. The everolimus C-0h blood trough level should still be kept ≥3 ng/mL. Everolimus should be discontinued if a C-0h blood trough level ≥3 ng/mL cannot be maintained due to toxicity or intolerable side-effects. The total daily dose should be adjusted by increasing or decreasing the dose depending on the C-0h blood trough level. If the C-0h blood trough level is <3 ng/mL, everolimus will be increased by doubling the dose and if the C-0h blood trough level is >8 ng/mL, the everolimus dose will be decreased by at least by 25 % of the daily dose. Interruption of study drug and/or temporarily everolimus C-0h blood trough level <3 ng/mL are up to the discretion of the investigator and the investigator has to assure for adequate immunosuppression, i.e. by compensating interruption and/or temporarily everolimus C-0h blood trough level <3 ng/mL by the temporary introduction of a higher exposure of tacrolimus.

Tacrolimus

Tacrolimus will be administered either orally in the capsule format or enterically with the liquid suspension for those who are unable to take oral medications at the time of transplant. Patients should remain throughout the study within the tacrolimus C-0h blood trough levels as pre-specified in the trial protocol. The tacrolimus dose should be adjusted if tacrolimus C-0h blood trough levels are outside the required drug target range. In case of severe tacrolimus toxicity, dose reductions below the target levels may be performed at the investigator's discretion. If tacrolimus is interrupted for more than 21 consecutive days or cumulative for more than 28 days, discontinuation of study medication should be considered. In particular, interruptions for an elective medical treatment (e.g. dental treatments) are not to be counted. Tacrolimus may be interrupted during antibody treatment of rejection episodes or elective surgery.

Mycophenolate mofetil

MMF will be administered either orally in the capsule format or enterically with the liquid suspension for those who are unable to take oral medications at the time of transplant. Patients should be administered and remain on MMF per institutional protocol. Dosage adjustments will be made based upon clinical practice/standard of care (SOC). Specifically, in subject randomized to group 2 (delayed everolimus), mycophenolate will be minimized as clinically indicated

Basiliximab Preparation and Administration

The 20mg dose of basiliximab will be given per labeled indication on day 0 and POD 4. It will be diluted in 50mL of sterile 0.9% sodium chloride and may be administered via central or peripheral line over 20 to 30 minutes

Rescue medication - Handling of acute rejection

In all suspected acute rejection episodes, regardless of initiation of anti-rejection treatment, a graft core biopsy will be performed preferably within 24 hours, latest within 48 hours, if clinically possible. Whenever possible, anti-rejection therapy should be postponed until a histological diagnosis of rejection is confirmed.

Acute rejections will be treated with bolus methylprednisolone (other corticosteroids are acceptable at an equivalent dose) according to local practice.

Other anti-rejection therapies (i.e. antibody therapy) should only be used in cases of steroid resistant rejections, or severe rejections with rejection activity index ≥7, or rare events of vascular rejection. A biopsy-proven acute rejection occurring >14 days after the last day of the course of antirejection therapy given for the previous episode will be counted as a distinct event.

Concomitant medications

Investigator will be diligent and avoid administrating therapy with drugs that potentiate tacrolimus-related nephrotoxicity.

In particular, the use of the following treatments is NOT allowed:

- Other investigational drugs and non-protocol specified immunosuppressant drugs.
- Drugs or substances that are strong inhibitors or inducers of CYP3A4. Certain drugs may need to be used if no alternative treatment is available. In such cases, everolimus should be interrupted for the duration of the treatment.
- If clinically significant proteinuria or nephrotic range proteinuria (protein-to-creatinine ratio ≥500 mg/m_2/24 hrs) occurs throughout the duration of the study, introduction of an angiotensin converting enzyme inhibitor or angiotensin receptor blocker should be considered as per local practice.

Cytomegalovirus (CMV) prophylaxis

Cytomegalovirus (CMV) prophylaxis will be administered according to local practice.

Pneumocystis pneumonia (PJP) prophylaxis

Prophylactic treatment for pneumocystis jiroveci pneumonia (PJP) consisting Bactrim® or equivalent (trimethoprim /sulfamethoxazole), starting when oral medication can be tolerated will be used as per local practice. Atovaquone or dapsone will be administered to patients unable to tolerate trimethoprim/sulfamethoxazole as per local practice.

Fungal Prophylaxis/Treatment

All patients will receive fungal prophylaxis and treatment according to local standard of care. Use of moderate inhibitors such as fluconazole will be permitted.

If the systemic use of a strongly interacting drug is required, study medication can be temporarily interrupted (or permanently discontinued).

Hepatitis B (HBV) prophylaxis

Prophylaxis for recurrent hepatitis B during the course of this study will be per institutional protocol.

Hepatitis C (HCV) treatment

Treatment for HCV disease can be done but not preemptively. Investigators treat HCV only when recurrent HCV disease has been documented, based on histological evidence as determined by the local pathologist. Therapies used for post-baseline HCV disease will be appropriately documented.

Lipid lowering medications

During the course of the study, the lipid profile will be monitored. Lipid lowering medications should be administered according to guidelines and local practice.

HMG CoA reductase inhibitors (e.g., pravastatin) will be administered according to local practice for the management of hyperlipidemia. Patients requiring treatment with this class of medication (especially lovastatin) should be monitored closely for signs of rhabdomyolysis, such as, dark-colored urine, fever, muscle cramps, pain, spasm, or stiffness, unusual tiredness or weakness. Lipid lowering therapy will be optimized before dosage reduction of study medication is considered.

Contraception

There are no adequate data from the use of everolimus in pregnant women. Studies in animals have shown reproductive toxicity effects including embryotoxicity and fetotoxicity. The potential risk for humans is unknown. Everolimus did not show genotoxicity in *in vitro* tests for gene mutations (bacteria and mammalian cells), and in an *in vitro* test and an *in vivo* mouse micronucleus assay for clastogenic activity. Therefore, male contraception is not indicated.

Other concomitant medication

Concomitant use of medications with a strong effect on CYP3A4 must be avoided, because of the risk for over- or under-exposure to everolimus. Investigators will instruct the subject to notify the study site about any new medications he/she takes after the start of the study medications.

Prohibited treatment

Uses of immunosuppressive agents such as azathioprine, sirolimus, and induction therapy with ALG, ATG, alemtuzumab or anti-tuberculosis agent as rifampin, and growth hormone therapy will not be allowed throughout the study.

Discontinuation of study treatment and premature patient withdrawal

Study treatment discontinuation

The investigators will discontinue study medication for a given patient or withdraw the

patient from study if, on balance, he/she believes that continuation would be detrimental to the patient’s well-being. In the absence of medical contraindication or significant protocol violation, every effort will be made to continue the patient on study medication

Reasons for study drug discontinuation include:

- Death.
- Graft loss and/or re-transplantation.
- Pregnancy
- Withdrawal of consent.
- Emergence of any serious adverse event (at the discretion of the investigator).
- Unsatisfactory therapeutic effect (e.g. repeated acute rejection).
- Administration of prohibited immunosuppressive medication.
- Abnormal laboratory value(s) not resolved after study treatment interruption for more than 21 consecutive days or more than 2 episodes longer than 10 days, everolimus C-0h blood trough level ≥3 ng/mL cannot be maintained due to toxicity.
- Abnormal test procedure result(s).
- Significant protocol violation.
- Any other protocol deviation that results in a significant risk to the patient's safety.
- Lost to follow-up.

Efficacy

Liver biopsy for suspected acute rejection

Liver biopsies will be performed in all cases of suspected acute rejection preferably within 24 hours and latest within 48 hours, whenever clinically possible. Whenever it is possible, anti-rejection therapy should be postponed until a local histological diagnosis of rejection is confirmed. The liver biopsy will be read by the pathologist according to the Banff classification of liver allograft rejection and will be used for patient management and treatment.

Acute rejection

All clinical suspected acute rejection episodes will be documented with the histological and clinical diagnosis specified.

Treated acute rejection is defined as a clinically suspected acute rejection whether biopsy proven or not, which has been treated and confirmed by the investigator according to the response to therapy.

Biopsy proven acute rejection and treated biopsy proven acute rejection

A biopsy proven acute rejection (BPAR) is defined as clinically suspected acute rejection confirmed by biopsy. In all suspected acute rejection episodes, regardless of initiation of anti-rejection treatment, a graft core biopsy will be performed preferably within 24 hours, latest within 48 hours whenever clinically possible. Whenever it is possible, anti-rejection therapy should be postponed until a local histological diagnosis of rejection is confirmed. The liver biopsies will be read by the pathologist according to the Banff classification of liver allograft rejection. The local histo-pathology results will be used for patient treatment and management. A treated biopsy proven acute rejection (tBPAR) will be considered as efficacy event if the local pathologist reading with a RAI score ≥3 of acute rejection index was applied and consecutive anti-rejection therapy was administered to the patient. These readings will be used to assess the efficacy endpoint at Months 3 and 5 after the start of everolimus based regimen.

Safety

Renal function

Serum creatinine, blood urea nitrogen, and serum cystatin C will be measured at all study visits and will be used to estimate the glomerular filtration rate by C/G (MDRD)

Statistical analysis

TBD

Projected Enrollment Period

March 22, 2019 through December 31, 2020

Patient Population

In a 2:2:1 scheme, 90 patients will be randomized at UCLA Medical Center between March 22, 2019 through December 31, 2020. Each patient will be followed for six months post-transplant.

Treatment Procedures

One of the investigators will obtain written informed consent for this study from all patients or their legal representative (LAR) prior to the performance of any protocol procedure. Should any patient who previously had surrogate consent provided by their LAR regain their capacity to provide consent on their own, we will collect consent directly from that patient. Per customary UCLA clinical practice, medical history will be taken, physical exam performed and labs drawn prior to transplant.

DRUG THERAPY

Group 1

Basiliximab

- Dose #1: 20mg IV within 2 hours of transplant
- Dose #2: 20mg IV Post-operative day #4

Tacrolimus (with basiliximab induction)

- Beginning day #5 post-transplant or when SCr $\leq$ 1.8 mg/dl (subjects off dialysis) to six months: 0.03-0.1mg/kg q12h PO to maintain whole blood trough concentration of 4-6ng/mL

Mycophenolate mofetil

- 500 mg po bid

Corticosteroids (SOC): Per UCLA protocol

Post-operative taper:

- Post-op day 1- methylprednisolone 50mg IVP Q6H
- Post-op day 2- methylprednisolone 40mg IVP Q6H
- Post-op day 3- methylprednisolone 30mg IVP Q6H
- Post-op day 4- methylprednisolone 20mg IVP Q6H
- Post-op day 5- methylprednisolone 20mg IVP Q12H
- Post-op day 6- methylprednisolone 10mg IVP Q12H
  until taking PO, then change to: prednisone 20mg PO QAM

Group 2

Basiliximab

- Dose #1: 20mg IV within 2 hours of transplant

- Dose #2: 20mg IV Post-operative day #4

Tacrolimus (with basiliximab induction)

- Beginning day #5 post-transplant or when SCr ≤ 1.8 mg/dl (subjects off dialysis) to POD 30: 0.03-0.1mg/kg q12h PO to maintain whole blood trough concentration of 4-6ng/mL
- POD 31; reduce to tacrolimus to 2-5ng/mL in presence of everolimus levels 3-8 ng/mL

Mycophenolate mofetil

- 500 mg po bid up to POD 30: reduce mycophenolate mofetil following achievement of steady state everolimus (POD 35) as clinically indicated

Corticosteroids (SOC): Per UCLA protocol

Post-operative taper:

- Post-op day 1- methylprednisolone 50mg IVP Q6H
- Post-op day 2- methylprednisolone 40mg IVP Q6H
- Post-op day 3- methylprednisolone 30mg IVP Q6H
- Post-op day 4- methylprednisolone 20mg IVP Q6H
- Post-op day 5- methylprednisolone 20mg IVP Q12H
- Post-op day 6- methylprednisolone 10mg IVP Q12H

until taking PO, then change to: prednisone 20mg PO QAM

Everolimus (delayed)

- Add by POD 30: 1 mg po bid and adjusted to maintain whole blood trough concentrations of 3-8 ng/ml.

Group 3 (control):

Tacrolimus (without basiliximab induction)

- Beginning day #1 post-transplant to six months: 0.03-0.1mg/kg q12h PO to maintain whole blood trough concentration of 5-12ng/mL
- Six months to one year: maintain whole blood trough concentration of 5-10ng/mL

Mycophenolate mofetil

- 500 mg po bid

Corticosteroids (SOC): Per UCLA protocol

Post-operative taper:

- Post-op day 1- methylprednisolone 50mg IVP Q6H
- Post-op day 2- methylprednisolone 40mg IVP Q6H
- Post-op day 3- methylprednisolone 30mg IVP Q6H
- Post-op day 4- methylprednisolone 20mg IVP Q6H
- Post-op day 5- methylprednisolone 20mg IVP Q12H
- Post-op day 6- methylprednisolone 10mg IVP Q12H
  until taking PO, then change to: prednisone 20mg PO QAM

Calcineurin Inhibitor Rescue Therapy

- If after 1 episode of acute rejection, full dose tacrolimus or cyclosporine may be used per UCLA liver transplant protocol.

Infectious disease

- Prophylaxis and treatment of all infectious diseases will be per UCLA liver transplant protocol

Basiliximab Preparation and Administration

The 20mg dose of basiliximab will be diluted in 50mL of sterile 0.9% sodium chloride and may be administered via central or peripheral line over 20 to 30 minutes.

Gently invert the bag to avoid foaming. Once the infusion is prepared, it should be administered IV within four hours. Basiliximab is stable for up to 24 hours at 2-8^{o}C. Infusion of basiliximab must be permanently terminated if the patient develops signs or symptoms suggestive of a severe allergic reaction

Acute Rejection Assessments and Procedures

- All patients with an unexplained deterioration in liver function (changes in total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, or γ-glutamyltransferase concentrations) or the appearance of clinical signs of rejection (fever, jaundice, pruritis, ascites, or hepatic tenderness) will receive a liver biopsy
- Treatment of acute rejection per standard clinical practice at UCLA

Definition of Rejection

The pathology department will classify any liver acute rejection episode per routine UCLA protocol.

Evaluation of CD_{25} cell count

- 5cc of blood will be drawn from the patient each day post-transplant until hospital discharge
- 5cc of blood will be drawn at each post-transplant clinic visit
- Monitoring of CD_{25} cell counts will take place over first 3 months post-transplant

Adverse Events

An adverse event is any adverse change from the patient's pre-treatment condition, which occurs during the course of the clinical trial, whether considered related to the treatment or not. Clinical adverse event will be graded on a 3 point scale (mild, moderate, severe) by the following definitions

1. mild- discomfort noticed, but no disruption of normal daily activity
2. moderate- discomfort sufficient to decrease or affect normal daily activity
3. severe- incapacitating - inability to work or perform normal daily activity

Adverse events will be monitored in the hospital and at clinic visits.

Criteria for Early Withdrawal

All patients have the right to discontinue the clinical trial at any time for any reason. However, all patients who have discontinued the trial will be followed for the entire 6 months post-transplant.

Collection of Data

Data on each enrolled patient will be kept on site at UCLA in a secured site. Subject privacy and confidentiality will be maintained. A computer generated database (coded encrypted data with access code) will maintain the files on each patient enrolled.

Study Completion

At study completion, results will be targeted towards the American Society of Transplantation and/or the journal American Journal of Transplantation, Liver Transplantation, or Transplantation

Institutional Review Board/Ethics Committee

This protocol and any other material provided to the patient will be provided to the Institutional Review Board/Ethics Committee. Approval from the IRB/EC must be obtained before initiation of this clinical trial and should be documented in writing. Any modifications made to the protocol must be submitted to the Committee.

Estimated Budget

~$3,500/patient

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