Carolinas HealthCare System
Center for Liver Disease

Spironolactone to prevent or delay calcineurin nephotoxicity after liver transplantation

Title: Investigator initiated study of spironolactone to prevent or delay calcineurin nephrotoxicity in liver transplant recipients

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1. **Specific Aim:**
   a. To determine if spironolactone decreases nephrotoxicity from calcineurin inhibitors in liver transplant recipients.
   b. To determine the best study of renal function in liver transplant recipients.

2. **Background:**

Chronic kidney injury affects up to 30% of liver transplant recipients after transplantation. Nephrotoxicity from calcineurin inhibitors (CNIs- tacrolimus, cyclosporine) is the leading cause of chronic kidney injury after liver transplantation. Strategies to reduced kidney injury include minimizing exposure to CNI's by using combination immunosuppressive regimens, such as low dose CNI and mycophenolate mofetil. Other strategies include switching from CNI to Mammalian target of rapamycin (mTOR) inhibitor. However, there may be barriers to using low dose CNI or mTOR inhibitor such as increased rate of rejection, CMV infection, or increased cost. Spironolactone is an antagonist of aldosterone, acting primarily through competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule. Animal models of CNI nephrotoxicity demonstrate decreased nephrotoxicity and kidney fibrosis in rodents treated with spironolactone. Small studies have demonstrated improved creatinine clearance in liver transplant recipients treated with spironolactone. In these studies spironolactone at low doses was well tolerated with acceptable rates of hyperkalemia.

3. **Study design:**

Randomized clinical trial of spironolactone versus no spironolactone in liver transplant recipients on calcineurin inhibitors (tacrolimus or cyclosporine).

- Subjects that are 3 weeks to 6 months post liver transplant with be screened for the study. After eligibility is established and informed consent document has been signed by the patient or representative, subjects will be randomized to spironolactone 25 mg daily, or no treatment. Non-English only speaking subjects will be consented with an interpreter. A total of 36 patients will be randomized (50/50), 18 to treatment and 18 to standard of care. Subjects that do not wish to enroll or do not meet the criteria for the main study may choose to participate in the sub-study if they are not allergic to iodine and if their GFR is greater 30 ml/min. 36 subjects may be enrolled in the sub-study to compare the currently used method of evaluating kidney function based on serum creatinine to other measures of creatinine clearance and kidney filtration rate (iothalamate GFR, 24 hour urine for creatinine clearance and protein, serum cystatin C, basic metabolic package and serum albumin.

Inclusion Criteria

- Liver transplant within 3 weeks to 6 months of study enrollment.
- Age 18-75 years old
- Proteinuria less than 3 g/24 hours
- Creatinine Clearance greater than 30 ml/min
- Negative pregnancy test for women of child bearing potential

Exclusion Criteria

- Patients on angiotensin converting inhibitors or angiotensin receptor blockers, digoxin, other drugs associated with hyperkalemia (dapsone can be substituted for sulfa-trimethoprim if needed at the discretion of the investigator)
- Potassium greater than 5.2 meq/L on screening labs, one occasion in a non-hemolyzed specimen,
- Prior intolerance to spironolactone
- Factors, that in the opinion of the investigator, would interfere with subject's compliance with the study
- Retransplantation
- Combined organ transplant-i.e. liver kidney, liver-heart
- Subjects who are anticipated to be placed on sirolimus or everolimus due to underlying condition (i.e. patients with HCC outside Milan criteria or with vascular invasion). Other

renal sparing protocols are allowed in including initial treatment with simulect, CNI reduction with mycophenolate mofetil

- Allergic to iodine

Patients will be monitored by SOC transplant protocol for up to 2 years.

For those subjects on treatment, if potassium stays less than 5.2 meq/L after 1 month on treatment, spironolactone may be increased to 50 mg daily at the discretion of the investigator.

4. Statistical analysis:

Mean GFR will be compared using unpaired Students' T test between groups and paired Students' t test within groups. If creatinine clearance is not normally distributed a nonparametric test will be used (Wilcoxon rank sum test) to compare creatinine clearance between groups. Sample size: 16 subjects in each group will be needed to detect a 10 ml difference in creatinine clearance with a power of 0.5 at $p \leq 0.05$.

5. Outcomes:

Primary outcome

- Change in creatinine clearance from screening to 1 year post randomization based on iothalamate GFR (glomerular filtration rate).
- Renal function tests will be compared to the iothalamate GFR to determine which best approximates the Glofil results.

Secondary outcomes

- Patient survival
- Graft Survival
- 6 month and 18 month creatinine clearance
- Dialysis
- Hyperkalemia (>5.5 mEq/L)
- Proteinuria as defined by > 3 g/24r

- Discontinuation for adverse events
- Conversion to renal sparing immunosuppressive regimen
- Number of subjects requiring sodium bicarbonate (NaHCO3)
- Calculation of CKD-EPI, CKD-EPI Cystatin, CKD-EPI-Cystatin-Creatinine, MDRD-4, MDRD-6 and 24 hour urine creatinine clearance at screening and 6, 12, 18, and 24 months. Comparison of the currently used method of evaluating kidney function based on serum creatinine to other measures of creatinine clearance and kidney filtration rate (CKD-EPI, CKD-EPI Cystatin, CKD-EPI-Cystatin-Creatinine, MDRD-4, MDRD-6, 24 hour urine creatinine clearance and iothalamate GFR).

6. Study Calendar of Events

	Screening	Randomization	Day 7	WK 2	WK 3	WK 4	MONTHLY until month 24	MONTHS 6,12,18, 24
		45 days from screening	±2 days	±2 days	±2 days	±2 days	± 5 days	± 2 weeks
History and physical	X							
Vitals signs (if recorded as part of the standard of care visit)	X	X	X	X	X	X	X	X
ECG	X							
CHEM-7	X	X	X	X	X	X	X*	
Albumin level (standard of care lab within 30 days)	X							X
24 HR creatinine clearance and 24 hour urine protein	X							X
Cystatin C	X							X

Iothalimate GFR **	X							ONLY 12, 24 MONTHS
Adverse events			X	X	X	X	X	
BLOOD FOR DNA ANALYSIS (Preferably collected at randomization, but may be collected at any post-randomization visit)		X						

*BMP weekly for 2 weeks if dose change in spironolactone or addition of NaHCO3

**Depending in the budget a subset of subjects may undergo iothalimate scans at baseline and 1 year

7. Safety and Monitoring Plan

Subjects in the study are liver transplant recipients who are regularly followed with blood work and physician and nurse visits. Standard of care blood work includes a complete metabolic panel, complete blood count, and tacrolimus level. These labs are obtained twice a week the first week after discharge from the hospital, then weekly until week 12 after discharge, then every 2 weeks until month 6, then monthly until year 2.

Transplant pharmacist, Bennett Noel, PharmD, and nephrologist, Chris Fotiadis, MD, have agreed to be available to discuss adverse events, and for advice and to help manage electrolyte abnormalities.

8. Adverse Event Management

The risks to subjects on spironolactone treatment are hyperkalemia and hypertension. As stated above patients will be monitored after liver transplant regularly per liver transplant protocol that follows standard of care. Any unscheduled labs will be paid for by the study. Subjects may also develop gynecomastia which will be treated by dose reduction and if not effective discontinuation of the spironolactone.

Protocol of elevated potassium

- If subject on spironolactone 50 mg daily and potassium is greater than 5.5 mg/mL then dose reduce spironolactone to 25 mg daily, and recheck potassium in 5 days. If potassium remains greater than 5.5 meq/L then patient will be discontinued from the study.
- If subject is on spironolactone 25 mg daily and potassium is greater than 5.5 meq/L, the spironolactone will be discontinued for 7 days and the potassium level will be rechecked. If the potassium level continues to be greater than 5.5 meq/L, then the subject will be discontinued from the study at the discretion of the investigator. If the subject's potassium is within normal limits, the investigator may resume the spironolactone at the investigator's discretion.
- Sodium Bicarbonate is allowed for subjects with bicarb (CO2) < 20 at 650 mg 2 pills twice a day for target bicarb 24 meq/L.

Treatment of hypertension

- Standard post-liver transplant protocol for hypertension will be followed with amlodipine as first line agent.
- Furosemide is allowed for hypertension or edema.
- Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are contraindicated.

Most women undergoing liver transplant are post-menopausal. As part of standard of care, women are advised against pregnancy the first 3 years after liver transplant. Urine pregnancy testing will be offered to women who suspect pregnancy as part of standard of care.

9. DNA Analysis

Subjects will be asked to consent for collecting and storing blood for DNA analysis. If a subgroup of subjects derive a benefit from spironolactone their DNA will be analyzed for polymorphisms known to be associated with nephrotoxicity from tacrolimus.

10. Compensation

Study medication and study related visits, labs, and iothalamate scan will be paid for by the study. Standard of care visits will be billed to insurance. Subjects will be made aware of standard of care versus study related visits, labs, and charges. Liver transplant recipients are seen by a physician the first week after discharge from the hospital after the liver transplant, and weekly for the first month. Subjects are seen every 2 weeks the second and third month after liver transplant. Then subjects are seen 6 months, 9 months and 1 year, then annually after liver transplant. A stipend will be given to subjects that are required to return to the Transplant Center for a visit which is outside of the standard of care. If the subject travels 60 miles or less, the subject will receive a 25 dollar stipend. If the subject travels greater than 60 miles, the subject will receive a 50 dollar stipend.

References:

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