UofL Liver Transplant Immunosuppression Protocol

UofL Induction Immunosuppression Therapy

No Renal Insufficiency	Renal Insufficiency (Cr Cr>2.0mg/dl or Cr CL ≤ 40 ml/min or requiring RRT - Basiliximab will be used at the discretion of the transplant surgeon and hepatologist)
IV Methylprednisone -500 mg bolus at graft reperfusion. -1 mg/kg per day Day 1-3 -0.5 mg/kg per day Day 4-6	**IV Basiliximab 20 mg** -Day 0 - end of OR or in ICU -Day 4 -Day 10-14 (optional)

UofL Maintenance Immunosuppression Day 0-59

	No Renal Insufficiency		Renal Insufficiency	All Patients	
Day post OP	**Preferred Tacrolimus (FK)**	**Alternate Cyclosporine (CSA)**		**Prednisone Taper (day 0-120)**	**Mycophenolate mofetil (MMF) aka CellCept**
0	Start NG, SL or PO 0.05 mg/kg BID (see calculated weight-based dose table protocol)	Start NG or PO 4 mg/kg BID (or as a continuous IV infusion at 2 mg/kg/day)	See Basilixumab Induction above	50 mg q12h	1 gm IV q 12h (given as a 2 hr infusion per dose)
1				25mg q 12 h	
2				See prednisone taper protocol	1000mg BID ↓ dose 50- 100% if: • WBC < 1.5 • platelets < 40 K • acute CMV infection • diarrhea 2/2 MMF
3 – 59	Titrate dose for trough level of 7 – 10 ng/mL	Titrate dose for trough level of 200–250 ng/mL	See Basilixumab Induction above **Day 4 - 31** If Cr drops <2 mg/dl (GFR>40) start FK titrate 6-8 ng/ml. **Day 4 - 31** - If Creat>2 (GFR>40), may continue CNI free with slower steroid taper, consider lower goal CNI or +/- 20mg basiliximab at day 10-14. **Day 31+**- if Creat>2 (GFR<40) consider Everolimus monotherapy (goal 5-8) or Everolimus (4-8)/FK (3-6)	See prednisone taper protocol	

UofL Maintenance Immunosuppression Day 60 and up

	No Renal Insufficiency		Renal Insufficiency	All Patients	
Day post OP	**Preferred Tacrolimus (FK)**	**Alternate Cyclosporine (CSA)**		**Prednisone Taper (day 0-120)**	**Mycophenolate mofetil (MMF) aka CellCept**
60	Trough of 5 – 8 ng/mL			See prednisone taper protocol	Withdraw at 2-4 months unless: • Pt at low levels of FK or CSA due to toxicity: Tac level < 6, CSA level < 100 • 1 rejection episode: treat through 4 months then reassess • 2 episodes of ACR or thymo: continue MMF x 1 year **SLKT continue CellCept indefinitely**
120	Trough of 4–7 ng/mL	Trough of 150–200 ng/mL		Discontinue unless tx for AIH, PSC, PBC or Re-tx - see prednisone taper protocol	**SLKT continue CellCept indefinitely**
1 year	Trough of 3-5 ng/mL	Trough of 50–150 ng/mL			**SLKT continue CellCept indefinitely**
2 years +	Trough of ~3 ng/mL	Trough 50–150 ng/mL			**SLKT continue CellCept indefinitely**

UofL Standard Prednisone Taper Protocol

Post-tx day	Standard Adult Prednisone Taper	
	mg/dose	Interval
0	50	q12h
1	25	
2 – 3	20	
4 – 6	15	
7 – 14	10	
15 – 20	15	qDay
21 – 29	10	
30 – 60	7.5	
61 – 90	5*	
91 – 120	2.5	
121	Discontinue	

Weight-based Calculations for Initial Tacrolimus Dose

Weight-based Calculations for Initial Tacrolimus Dose

Weight (kg)	Tacrolimus Dose
< 40	1.5 mg BID
40-49	2.0 mg BID
50-59	2.5 mg BID
60-69	3 mg BID
70-79	3.5 mg BID
80-99	4 mg BID
>=100	4 mg BID*

UofL Immunosuppression protocol for Everolimus or Sirolimus

Candidates for Therapy
-Patients with significant calcineurin inhibitor (CNI) toxicity without contraindication to mTOR therapy. -Patients at risk of CNI renal toxicity greater than 1-month post-transplant as a combination therapy approach with CNI dose reduction
Contraindications for Therapy
-Previous intolerance to mTOR inhibitor -Significant pulmonary disease especially interstitial lung disease or recurrent pneumonia -Severe anemia or other cytopenia not related to renal insufficiency -Significant proteinuria (>1 g per 24 hours)

UofL Protocol for Initiation of Therapy with mTOR

-Obtain baseline CXR, hematologic, liver, and renal profile, CNI drug level, UA for protein (24-hour collection if positive and Nephrology consult if confirmed), urine Protein/Creatinine ratio, baseline lipid profile, Doppler US of the liver

-UA for protein/creatinine ratio Q. 3 months for 1 year, unless otherwise directed by nephrology team based on pre-treatment studies. Consider extending interval of urinalysis to Q. 6 months if no proteinuria at 1 year.

-Monthly lipid profile for first 3 months of therapy, then obtain additional testing based on severity of hyperlipidemia and response to treatment

-If considering discontinuation of CNI, initiate 10 mg prednisone or equivalent additional immunosuppressive medication to decrease risk of rejection with everolimus or sirolimus monotherapy

-Follow up hepatic artery imaging after 3 months of therapy in absence of indication for earlier imaging. If within acceptable limits, image per standard post liver transplant protocol

UofL Protocol for Initiation of Therapy with mTOR

Everolimus (Zortress®) start at 0.5-1 mg by mouth twice daily

-Do not prescribe Afinitor - this is oncology dosing
-Obtain everolimus levels 5-7 days into therapy.
-Monitor everolimus levels weekly for 6 weeks after initiation of therapy, then every other week for 12 weeks, then monthly thereafter if stable
-Adjust dose of everolimus by 0.5-1 mg twice a day to obtain target level of 4-8 ng/mL based on clinical indication
-Once target level obtained, reduce CNI therapy to lowest tolerated level:
    -Tacrolimus target level 3-6 ng/ml
    -Cyclosporine target level 30-100 ng/ml

Sirolimus, start at 1-2 mgs by mouth daily

-Obtain sirolimus levels 5-7 days into therapy.
-Monitor sirolimus levels weekly for 6 weeks after initiation of therapy, then every other week for 12 weeks, then monthly thereafter if stable

UofL mTOR Protocol Target Levels

Sirolimus				
	Day 0-21	**Day 22-120**	**Day 121-365**	**After day 365**
Sirolimus/Rapamycin (Rapamune®) – > day 31+				
Target level monotherapy (ng/ml)	N/A	10-14	8-14	8-12
Target level dual therapy with CellCept** (ng/ml)	N/A	8-12	7-10	6-10
Everolimus				
Everolimus (Zortress®) do not start until day 31+				
Target level (ng/ml)†	N/A	4-8	4-8	4-8

** reduce CellCept to 500 mg BID; discontinue if cytopenias develop rather than reducing rapamycin

Discontinue everolimus/sirolimus therapy and resume previous immunosuppressive

- Severe rejection requiring multiple courses of intravenous corticosteroids
- Severe anemia or cytopenias requiring multiple transfusions or growth factor supplementation
- Severe mouth ulcers or GI distress
- Documented pneumonitis not due to infectious process
- Major surgery with risk for inhibition of wound healing (if elective surgery)
  - Initiate alternative immunosuppression and stop everolimus/sirolimus 3 weeks before surgery
  - May consider reinstitution of everolimus/sirolimus after recovery from surgery between 6 and 12 weeks based on tolerance of CNI therapy and extent of surgery
- Skin rash or allergic reaction suspected to be due to everolimus/sirolimus
- Medical complications of severe hyperlipidemia not responsive to therapy
- Abnormal imaging suggestive of hepatic artery disorders

UofL Treatment of Rejection

Management of Mild Rejection (Grade I & RAI < 4) HCV RNA positive patient (rare with DAA)
Increase tacrolimus dose to high therapeutic range (10- 15 ng/ml)
For renal sparing protocol patient – start low dose tacrolimus (target levels 2-8)
If increased tacrolimus not tolerated, hold steroids at current dose/slow steroid taper.
Repeat Biopsy if not responding and rejection suspected
Management of Mild Rejection (Grade I & RAI < 4) HCV negative patient
Treat as per moderate to severe rejection protocol (see next).
Increase tacrolimus dose to higher therapeutic range
If renal sparing protocol, pulse steroids only, no additional tacrolimus.

Treatment of Mild, Moderate, or Severe Acute Allograft Rejection (ACR) #1

Treatment Day(s)	Solu-Medrol Dose	Oral Prednisone Dose	Diagnosting Testing QOD (M-W-F)
1	1000 mg IV	-	-
2		240 mg	Protocol (or alternate) labs
3		180 mg	Protocol (or alternate) labs
4		120 mg	Protocol (or alternate) labs
5		80 mg	Protocol (or alternate) labs
6		60 mg	Protocol (or alternate) labs
7		40 mg	Protocol (or alternate) labs; Repeat Liver Biopsy
8-14		20 mg	Protocol (or alternate) labs
15-21		15 mg	Protocol (or alternate) labs
22-28		10 mg	Routine
29-Indefinitive		5 mg	Routine

Protocol labs: CBC with diff, CMP, INR, Drug Level daily while hospitalized then at least QOD for duration of therapy, then twice weekly.

Day 7: Liver Biopsy

Infection Prophylaxis for Protocols #1, #2 and #3: Anti-infection Prophylaxis x 3 months: Valgancyclovir 900 mg/d + Bactrim 160/800 mg/d or Atavaquone 1500 mg/d + Fluconazole 400 mg/d (at discretion of provider based on infection risk and side effects including cytopenias)

Consider lower dose of steroids (#1) or alternative treatment for patients that are severely compromised or at treating physician's discretion

Treatment of Mild, Moderate, or Severe Acute Allograft Rejection (ACR) #2

Treatment Day	Solu-Medrol Dose	Oral Steroid Dose	Diagnostic Testing QOD (labs typically on M-W-F)
1	1000 mg IV	As usual	None
2	1000 mg IV	As usual	None
3	1000 mg IV	As usual	Protocol (or "alternate") labs
4	None	As usual	Protocol (or "alternate") labs; repeat liver biopsy

Protocol labs: CBC with diff, CMP, INR, Drug Level daily while hospitalized then at least QOD for duration of therapy, then twice weekly.

Day 4: Liver Biopsy

Infection Prophylaxis for Protocols #1 and #2: Anti-infection Prophylaxis x 3 months: Valgancyclovir 900 mg/d + Bactrim 160/800 mg/d or Atavaquone 1500 mg/d + Fluconazole 400 mg/d (at discretion of provider based on infection risk and side effects including cytopenias)

Consider lower dose of steroids (#1) or alternative treatment for patients that are severely compromised or at treating physician's discretion

Treatment of Mild, Moderate, or Severe Acute Allograft Rejection (ACR) #3

Treatment Day	Solu-Medrol Dose	Oral Steroid Dose	Diagnostic Testing QOD (labs typically on M-W-F)
1	1000 mg IV	As usual	
2	None	As usual	Protocol (or “alternate”) labs
3	1000 mg IV	As usual	None
4	None	As usual	Protocol (or “alternate”) labs
5	1000 mg IV	As usual	None
6	None	As usual	Protocol (or “alternate”) labs; repeat Liver Biopsy

Protocol labs: CBC with diff, CMP, INR, Drug Level daily while hospitalized then at least QOD for duration of therapy, then twice weekly.

Day 6: Liver Biopsy

Infection Prophylaxis for Protocols #1, #2 and #3: Anti-infection Prophylaxis x 3 months: Valgancyclovir 900 mg/d + Bactrim 160/800 mg/d or Atavaquone 1500 mg/d + Fluconazole 400 mg/d (at discretion of provider based on infection risk and side effects including cytopenias)

Consider lower dose of steroids (#1) or alternative treatment for patients that are severely compromised or at treating physician’s discretion

UofL Thymoglobulin Protocol for Steroid-Resistant Liver Allograft Rejection

THYMOGLOBULIN DOSE

Dose: 1.5 mg/kg IV. Consider reducing dose or holding if platelet count <50,000 or WBC <2000. Given on days 1, 2, 3, 5, 7

Route: Usually given by central line as a 4-6 hours infusion. Can be given peripherally over 6 hours if specially prepared with heparin and hydrocortisone. Notify pharmacy and indicate on the order.

Routine Prophylaxis: Steroids: 250 mg IV Solu-Medrol before first dose, 30 mg prednisone PO on days 2-3. Benadryl 50 mg IV or PO and Tylenol 650 mg PO 30 minutes before every thymoglobulin dose. The Benadryl dose may be reduced by 50% after symptoms subside in 2-3 days. Bactrim SS tabs daily during the course of thymoglobulin therapy, then 3 months thereafter. Valganciclovir for CMV prophylaxis during course and then 3 months thereafter.

POST-DOSE ORDERS

Day 1: VS q 15 min x 2 hrs, q 30 min for 2 hrs, q 4 hrs if stable. Temp hourly x 3, then routine prn.

Day 2: VS q 15 min x 1 hr, q 4 hrs. Temp q 4 hrs prn.

UofL Immunosuppression During Thymoglobulin

Immunosuppression during Thymoglobulin Therapy
Prednisone: Continue usual dose. May drop to 20 mg bid if the patient on higher dose **Mycophenolate/mofetil:** Continue as usual, adjusting as necessary if cytopenia or hold as clinically indicated **Tacrolimus or cyclosporine:** Continue as usual throughout the thymoglobulin course.
Follow-Up Tests
Protocol labs: Daily CBC with diff, CMP, INR Drug level while hospitalized then at least QOD for duration of therapy, then twice weekly. Check T+B Lymphocytes subsets after the third dose. **Day 8:** Liver Biopsy

Options of Treatment of Acute TCMR

Severity of Acute TCMR	Treatment
Mild Acute TCMR	Increase CNI level + /- add anti-metability (mycophenolate) or mTORi
Moderate and Moderate to Severe TCMR	-Pulse steroid SoluMedrol 500-1000 mg IV x 3 days + slow oral steroid taper + Increase CNI level +/- add anti-metability (mycophenolate) or mTORi, vs -**SoluMedrol 1000 mg IV x 1, then oral Prednisone (in mg) 240 x 1d, 180 x 1d, 120 x 1d, 80 x 1d , 60 x 1d, 40 x 1d, 20 x 7d, 15 x 7d, 10 x 7d, 5 daily.** Anti-infection Prophylaxis x **3 months** Valgancyclovir 900 mg/d + Bactrim 160/800 mg/d or Atavaquone 1500 mg/d + Fluconazole 400 mg/d
Failure to Respond or Severe Cholestatic TCMR	Anti-thymocyte globulin Anti-infection Prophylaxis x **6 months** Valgancyclovir 900 mg/d + Bactrim 160/800 mg/d or Atavaquone 1500 mg/d + Fluconazole 400 mg/d

Antibody Mediated Rejection (AMR)

Rare: less than 1% of Transplants (< 5% of sensitized patients).

Consider it if non-responding Acute TCMR therapy.

Mild Acute AMR is treated with Steroid boluses 500 – 1000 mg SoluMedrol/d IV x 3 + Steroid taper or lymphodepletion therapy.

Moderate-Severe Acute AMR treated with plasmapheresis, IV immunoglobulins or B-cell depletion with Rituximab or bortezomib.

No clear therapy for Chronic AMR.

Antibody Mediated Rejection When to Consider

RISK FACTORS:

- Refractory Rejection (steroid resistant);
  - Monitor Donor Specific Antibodies (DSA) after severe TCMR, steroid-resistant TCMR, and in unexplained allograft dysfunction
- Re-transplant (sensitized).
- HLA mismatch, positive x-match.
- Necrosis or vascular injury.

TREATMENT: In evolution; plasmapheresis + IVIG + immunosuppression changes.

PROPHYLAXIS:

- Blood transfusion minimization in cirrhosis.
- Adherence to immunosuppression regimen.

Antibody Mediated Rejection Features

Clinical Features

- Unknown Incidence
- Due to ABO incompatibility and Donor Specific Antibodies (DSAs)
- May occur hours, days or months Post-OLTx
- Elevated liver enzymes, elevated PT/INR, decreased platelet count, low serum complement.
- High serum Donor Specific Antibodies (MFI > 1000).

Histologic Features

- Endothelial cell injury within the vasculature of the portal tracts (endothelial hypertrophy, endotheliitis with intraepithelial and marginating eosinophils, macrophages, lymphocytes, and neutrophils)
  - Bile ductular proliferation, scattered apoptotic bodies within the lobules, centrizonal swelling of hepatocytes, and canalicular cholestasis.
- Diffuse and strong C4d deposition in the portal veins, capillaries, and periportal sinusoidal endothelium involving most of the portal tracts.
- Exclusion of other causes of similar injury

Acute Antibody Mediated Rejection (AMR)

Clinical Manifestations	Histology	Definition Criteria
•Rapid allograft failure, hemorrhagic necrosis •Graft injury with refractory thrombocytopenia, hyperbilirubinaemia, low serum complement levels. •Elevated transaminases despite optimal donor liver quality	•Portal microvascular endothelial cell hypertrophy •Microvasculitis/capillaritis with monocytes, eosinophils and/or neutrophils •Portal/peri-portal edema •Microvascular injury involving central veins •Fibrin deposition, red blood cells seen in sub-sinusoidal regions •Cholestasis, ductular reaction	•Compatible Histology •Elevated DSA (> 1000); MFI > 3000 is associated with clinical outcomes. DSA with MFI Sum >20,000 has increased fibrosis risk. •Diffuse C4d deposition of microvasculature in ABO-compatible tissues, or portal stroma in ABO-incompatible tissues •Exclusion of other liver diseases or complications that can cause similar patterns of injury

Chronic Antibody Mediated Rejection (AMR)

Clinical Manifestations	Histology	Definition Criteria
•Can be associated with graft injury and/or advanced fibrosis without clear etiology, sometimes in the setting of cyclosporine use or HCV infection •Development of portal hypertension after transplantation •Abnormal liver tests during immunosuppression weaning	•Mild portal/peri-portal/peri-venular inflammation •Mild interface hepatitis •Dense portal fibrosis with collagenisation •Obliterative portal venopathy •"V" lesions (inflammation, necrosis or obliterative arteriopathy in the absence of significant portal or peri-venular activity). •Periductal fibrosis, ductopenia	•Compatible Histology •Positive DSA (> 1000) within 3 months of biopsy. MFI > 3000 is associated with clinical outcomes. DSA with an MFI Sum >20,000 has an increased risk of fibrosis. •Focal C4d positivity (>10% portal tracts) •Exclusion of other causes of graft injury

Antibody Mediated Rejection Treatment

Treatment of **Acute** Antibody Mediated Rejection

- **First-line:** conventional rejection therapy (tacrolimus and corticosteroid-based therapy) including IV Solu-Medrol 1 gm + tapper. Repeat biopsy and DSA.
- **Second-line therapy:** plasma exchange every other day and periodic low-dose IVIG (100–500 mg/kg) or High-dose IVIG (2-5 gm/kg) for a minimum of 5 sessions. Repeat biopsy and DSA.
- **Third-line Therapy:** In moderate to severe acute AMR persistent in biopsy after second-line therapy, consider anti-CD20 (Rituximab) agents or proteasome inhibitors (Bortezomib) up to 4 times each, alone or sequential. Repeat Bx and DSA to decide to repeat.
- **Re-Transplantation:** assess DSAs prior to consideration of re-transplantation in order to guide clinical management should allograft dysfunction, rejection, or other complications occur. Anti-Thymocyte globulin before Re-Tx?

Treatment of **Chronic** Antibody Mediated Rejection

- IV Solu-Medrol IV 1 gm + tapper + keep on Tacro > 5 ng/mL + Prednisone.
- In patients with plasma cell-rich rejection, treatment with a purine analogue or mycophenolate mofetil can also be considered.
- Focus on corticosteroid/tacrolimus compliance, more frequent laboratory and histologic surveillance, and the consideration of re-transplantation. Assess DSA before re-Transplant.

Risk of Rejection in OLTx with Different Regimens

Regimen	Acute (ACR)	Chronic (Ductopenic)
Pred + Aza	85 %	25 %
Pred + CyA	70 %	15 %
Pred + Tacr	55 %	6 %
Pred + CNI + MMF	45 %	1 %
Tacr + Rapa	18 %	1 %

Chronic T-Cell Mediated Rejection

Occurs to 2-5% of adult patients (up to 16% in children).

Evolves from severe or persistent Acute TCMR

Slow, indolent process months to years after transplantation.

Rise of cholestatic enzymes.

Has immune & non-immune components; poorly defined.

Causes ischemic injury and paucity of bile ducts.

Characterized by arteriole thickening & interstitial fibrosis.

Loss of small bile ducts +/- neo-intimal proliferation with ***obliterative vasculopathy*** (foam cell obliterative arteriopathy).

- Bile duct loss > 50%, or
- Bile duct atrophy/pyknosis in the majority of bile ducts, or
- Foam cell obliterative arteriopathy.

Risk Factors for Chronic TCMR

- Multiple or Severe A cute TCMR episodes.
- Severe AR with Centrilobular Necrosis.
- Non-compliance.
- Under immunosuppression.
- Autoimmune etiology
- Donor/ Recipient sex mismatch.
- Re-transplantation for rejection

Chronic TCMR Prognostic Factors

Bile duct loss > 50% of portal tracts

Foam cell clusters within the sinusoids.

Severe, bridging, perivenular fibrosis.

Severe hyperbilirubinemia (TB >/= 25)

- Bili of </= 4.6 has higher resolution.

Management of Chronic TCMR

Switch CyA to TAC while TB < 10 mg/dL

- 50% success
- Ductular reaction is a positive feature.

Higher TAC levels

Add mTOR-I or MMF

- Consider infection prophylaxis

Avoid over-immunosuppression with late cases of liver synthetic dysfunction.