Immunosuppression and Rejection

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Immunosuppression and Rejection in LT

- Mechanism of Action and Pharmacokinetics of Immunosuppressive Medications
- Perioperative drug toxicity
- Immune Complications (rejection, GVHD, alloimmune/de novo autoimmune diseases)
INDUCTION AND MAINTENANCE IMMUNOSUPPRESSION

Kim et al, AJT SRTR Report

[Diagram showing immune system regulations]

T cell

Costimulatory Signals
CTLA-4 Ig
Anti-CD3
ATG
Anti-CD52

Antigenic Signal

APC

Anti-CD3

1

TCR

Ca^{2+}

CsA FK506

Activated Calcineurin

NFAT

IL-2

Steroid

NFAT

IL-2 GENE PROMOTOR

IL-2R Inhibitor

Sirolimus

Everolimus

De novo

purine

biosynthesis

Aza

M

G1

G2

MMF

MMF
Cyclosporine

- Most effective against T cell-dependent immune mechanisms
- Forms a complex with cyclophilin and this binds calcineurin.
- Inhibition of Ca2+ dephosphorylation of NFAT (Nuclear factor of activated T cells)
  - Prevents NFAT entering the nucleus
- Inhibits antigen-triggered signal transduction in T lymphocytes by blocking lymphokine production (IL-2, 3, 4, 5; IFN)
- Excreted in bile
- ½ life = 8 hours (range 5-18 hours)

FK-506 (Tacrolimus)

- Another bacterial derivative (Streptomyces)
- Binds to FKBP-12 (immunophilin)
- Forms a complex and inhibits calcineurin phosphatase.
- 1994 (US multicenter study group; comparison with Sandimmune) – less rejection and steroid-resistant rejection
- Like CSA, it has Cytochrome P450 metabolism but is about 20-25x more potent
- Excreted in bile
- ½ life = 11 hours
CNI side effects

- Nephrotoxicity (Early reversible, Late irreversible)
- Neurotoxicity (TAC>CyA) – ranges from seizures, PRES, HA, tremors
- Diabetes (TAC>CyA)
- Hyperlipidemia, Hypertension
- Hair loss (TAC), gain (CyA)
- Rare: HUS (TAC>CyA)

CNI Renal Sparing Studies

- Delay and reduction of CNI exposure minimizes AKI but typically requires antibody induction
- Early (1-6 months post-LT) CNI reduction, typically in combination with non-nephrotoxic agents, may improve/stabilize renal function
- There is evidence that MMF and concurrent reduction in CNI therapy results in improvement of renal function even when performed > 1 year post-LT
- The liver allograft provides partial immunologic protection of a simultaneous renal allograft from the same donor.

Levitsky, O'Leary et al. AJT 2016
Mycophenolate Mofetil

- Active form mycophenolic acid
- Noncompetitive inhibitor of Inosine monophosphate dehydrogenase
- Interferes with guanine nucleotide synthesis and thus purine synthesis
- Potent inhibitor of B and T cells
- Main side effects GI, marrow suppression, GVH-like gut lesion
- Stop if considering pregnancy (teratogenic)

Sirolimus/Everolimus

- Inhibits mTOR (cell cycle regulatory protein)
- Like Tacrolimus, also bind to FKBP
- Unlike Tac, the mTOR FKBP complex - no calcineurin inhibition
- The calcineurin inhibition action of CSA and FK leads to increased endothelin and TGF-β (mediators of acute and chronic renal injury)
  - Not with mTOR (opposite)
- Sirolimus – black box warning for increased risk of HAT and death in LT recipients
- Everolimus – indicated in combo with low dose tac > 30 days post-LT to spare renal function
mTOR-I Side Effects

- Pancytopenia
- Impaired wound healing
- Hepatic artery thrombosis
- Hypertriglyceridemia
- Other SE (oral and GI ulcers, edema, proteinuria, rare pneumonitis)
- Side effects often high trough dependent
- SRL ½ life = 63 hours
- EVL (BID) ½ life = 30 hours
- Excreted in bile
Immunosuppression Summary

- Centers start with CNI (Tac >>> CSA)
- 25% use induction (ATG, IL-2R antagonist), mainly for renal sparing
- >50% use adjunctive MMF at the onset
- 90% use corticosteroids with taper by 3-6 months; steroid-free much less common (induction + CNI + MPA)
- mTOR-I increased utilization after 1-3 months for renal sparing

Assay Methods for Drug Levels

- Drugs are concentrated in RBCs
- CNIs, mTOR: immunoassays (ELISA)
- Standard of care
  - Pre-dose trough levels
  - Poor correlation with degree of over- or under-immunosuppression
Pharmacogenomics: Drug Metabolism

• CNIs, mTOR inhibitors, steroids all metabolized by the cytochrome P450 3A family (3A4, 3A5)
  – intestinal, liver, T/B /NK cells, monocytes

• Substrates for the efflux transporter P-GP
  – multidrug resistance-1 gene (MDR1/ABCB1)

<table>
<thead>
<tr>
<th>Interactions between Immunosuppressive Agents and Other Medications</th>
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<tbody>
<tr>
<td><strong>Drugs that increase CNI and mTOR trough concentrations (block CYP3A4/5):</strong></td>
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<tr>
<td>Macrolides: clarithromycin, erythromycin, azithromycin</td>
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<tr>
<td>Antifungals: fluconazole, ketoconazole,itraconazole, voriconazole, clotrimazole</td>
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<tr>
<td>Calcium channel blockers: verapamil, dilitiazem, nifedipine</td>
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<tr>
<td>Others: metoclopramide, danazole, HIV/HCV protease inhibitors, grapefruit juice</td>
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| **Drugs that decrease CNI and mTOR trough concentrations (induce CYP3A4/5):** |
| Antibiotics: rifampin, rifampicin, rifabutin |
| Anticonvulsants: phenytoin, phenobarbital, carbamezazine |
| Others: St. John’s Wort |
Rejection

- Acute Rejection (T cell Mediated Rejection: TCMR)
  - Early, classic
  - Late, atypical
  - Management
  - New data that acute rejection is associated with higher risk of graft failure and death, incrementally worse with time from transplant
- Chronic Rejection
  - Vascular; Ductopenic
  - Management
- Antibody Mediated Rejection (AMR)


Classic acute TCMR

- Generally 5-30 days, 10-20% of patients
- Higher in autoimmune patients, females, young age, DR mismatches, retransplant
- Rare clinical manifestations unless late diagnosis - fever, abdominal pain, ascites, leukocytosis, eosinophilia
- Biochemical abnormalities non-specific (GGT)
MILD TCMR = <50% of portal tract involvement

TCMR ENDOTHELITIS AND DUCT INJURY
MODERATE TCMR = >50% portal tract involvement

SEVERE TCMR = >50% portal tract involvement with central vein involvement/necrosis
Management of TCMR

- Mild TCMR can be treated with increased maintenance immunosuppression without steroids
- Treat with corticosteroids for moderate to severe TCMR
  - Severe histological and clinical AR – consider initial ATG
- ATG for refractory cases and consider AMR (C4d staining and DSA testing)
- Investigate the reason for TCMR
- Optimize underlying immunosuppression if inadequate
- If already optimized at the time of TCMR, add on 2nd agent
- Consider long term prednisone in autoimmune patients and others with at least 2 episodes or a severe TCMR

Charlton, Levitsky et al. ILTS consensus statement. Transplantation 2018 May

Chronic Rejection

- Indolent, progressive obliterative arteriopathy + intrahepatic cholangiopathy/loss
- 5% of liver recipients and rarely reversible
- Rise in cholestatic enzymes
- Occurs typically in the following patients:
  - Multiple TCMR bouts
  - Severe TCMR with centrilobular necrosis
  - Noncompliance
  - Under-immunosuppression
CR

- Need 8-10 portal tracts (>2 cm piece)
- Minimal criteria for CR are any of following:
  - bile duct loss affecting greater than 50% of the portal tracts
  - the presence of bile duct atrophy/pyknosis, affecting a majority of the bile ducts, with or without bile duct loss
  - foam cell obliterative arteriopathy

Associated with allograft failure:
- bile duct loss >50% of portal tracts
- severe (bridging) perivenular fibrosis
- foam cell clusters within the sinusoids
- Severe hyperbilirubinemia
  - Graft failure median TB 25.5 vs. resolution 4.6*
  - If persistent and associated with synthetic dysfunction or portal HTN, not reversible

Prognosis of CR

CHRONIC REJECTION

FOAMY ARTERIOPATHY

DUCTOPENIA

Cytokeratin 19 stains biliary epithelium (CK-19)
Management of CR

- Switch cyclo to TAC in early CR (TB <10)
  - <50% success*
  - Ductular reaction is a positive feature
- Add on mTOR-I or MMF but little data
- Consider infection prophylaxis
- Avoid over-immunosuppression with late cases of liver synthetic dysfunction


When to Consider AMR?

- Refractory rejection (steroid resistant)
- Retransplant patient (sensitized)
- HLA mismatch, positive X-match
- Necrosis/Vascular Injury
- SLK (kidney)
- Unexplained chronic fibrosis or inflammation
- Diagnosis: Histologic findings (next slides), C4d staining in the venules, presence of DSA

Demetris et al. AJT Oct; 16 (10): 2816-2835
Acute Antibody-Mediated Rejection

- Portal edema, ductular reaction, neutrophils
- Periportal necrosis
- Sinusoidal inflammatory infiltration

Immunostaining for C4d

- Portal Vessels = most frequent
- Portal Stroma (focal or diffuse)
- Bile Duct
- Sinusoids
  Associated with lobular inflammation?
Management of AMR

- Borrowed from other organ transplants (kidney) which also do not have data-driven guidelines for therapy
- Antibody binding agent: IVIG
- Antibody removing therapy: Plasmapharesis
- Antibody production inhibitor: Rituximab (anti-CD20), Bortezomib (proteasome inhibitor – inhibits plasma cells)
- Complement inhibition (blocks injury from DSA): Eculizumab

Chariton, Levitsky et al. ILTS consensus statement. Transplantation 2018 May

Variants of Rejection

- Plasma cell hepatitis
  - Early, often with negative autoantibodies (>60%)
  - Centrilobular necrosis associated
  - ? Antibody mediated rejection

- Idiopathic posttransplantation hepatitis
  - 5-15% will have fibrosis progressing to cirrhosis over 10 years
  - Autoantibodies and plasma cells associated with progression

- Late rejection (> 6 months)
  - May be histologically different
  - Lobular activity, interface hepatitis, central perivenulitis (without endothelitis);
    Can also mimic PCH
  - Possible evolution to CR with hepatocyte dropout in the perivenular regions and loss of inflammation

PLASMA CELL HEPATITIS

LT Recipients at Higher Risk for Immune-Mediated Injury

- Autoimmune liver disease
- Previous episodes of rejection/late ACR
- Necessitated minimization of maintenance immunosuppression
  - PTLD
  - Setting of cancer chemotherapy
  - Sepsis
  - Attempt at immunosuppression withdrawal
- Non-adherence (standard deviation of trough levels)
- Presence of donor-specific HLA antibodies
- Presence of certain viral infections, i.e. CMV, HCV

Banff Working Group on Liver Allograft Pathology; Liver Transpl 2012
Management of Immunosuppression in the High-Risk Patient

- Ongoing regular laboratory testing
- Clinician awareness of ongoing risk
- Patient education to seek medical advice for:
  - viral syndromes
  - illnesses affecting medicinal absorption
  - addition of new medications/herbs
  - change to generic preparation
- Consideration of protocol liver biopsy
- Maintenance corticosteroids in patients with AIH

GVHD post-LT

- <1% but >80% mortality (sepsis)
- Typically 2-8 weeks post-LT
- Triad of rash, cytopenia, diarrhea… and normal allograft function
- Diagnosis: FISH X-Y chimerism, PBMC donor-recipient chimerism, skin biopsy. GI biopsy rarely needed
- Treatment: high dose steroids, lymphodepletion, stop IS (host vs. graft response against donor-reactive cells), stem cell transplant