# Liver Transplant Immunosuppression and Rejection

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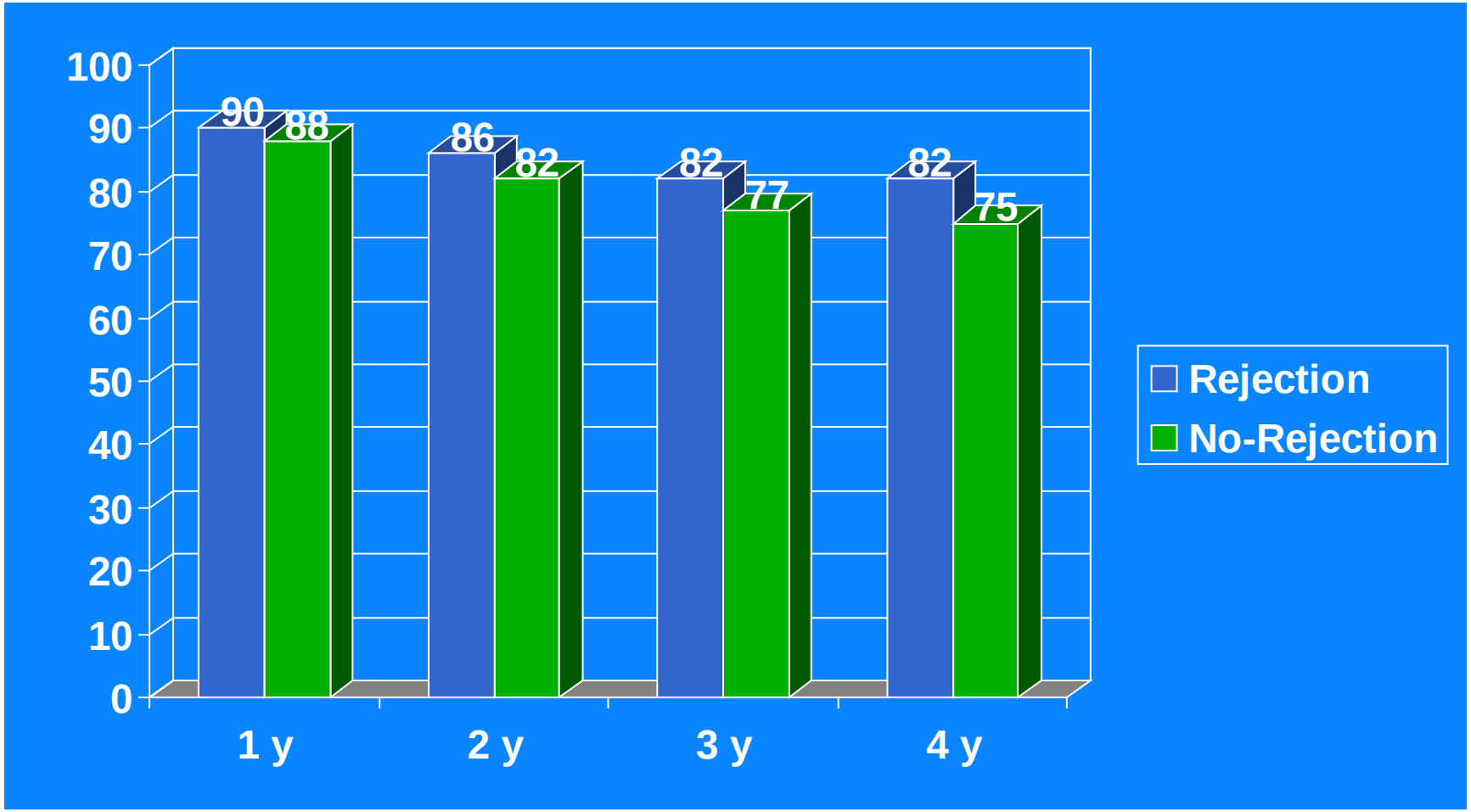
# Background: Rejection, Graft loss and Survival

# Survival vs Rejection in OLTx




Rejection/No-Rejection RR = 0.7

# Impact of ACR Therapy on Survival

| Patient | Therapy | RR Mortality |
|---|---|---|
| Non-HCV | Steroids | 0.5 |
| HCV | Steroids | 2.9 |
| HCV | OKT3 | 5.4 |

**DO NOT TREAT MILD REJECTION IN HCV**

# Causes of Late Liver-Graft-Loss

| | |
|---|---|
| **Rejection** | **< 5 %** |
| **De-novo Malignancy** | **15 %** |
| **Infections** | **16 %** |
| **Cardiovascular Disease** | **20 %** |
| **Recurrent Disease** | **35 %** |

Excessive Immunosuppression causes more problems than rejection

# Long-Term Complications of Immunosuppression

| | |
|---|---|
| **Renal Dysfunction** | **80 %** |
| **Hypertension*** | **70 %** |
| **Hyperlipidemia*** | **50 %** |
| **Diabetes Mellitus*** | **20 %** |
| **Bone Disease*** | **20 %** |
| **Skin Cancer** | **40 %** |
| **Lymphoma** | **4 %** |

* Less if Steroids are withdrawn shortly after 3 months

# IMUNOSUPPRESSIVE REGIMENS

# Immunosuppression Minimization (ISM)

Is best to personalize Immunosuppression considering recipient characteristics, etiology, and alloimmune activation.

Best started at or after 3rd post-Tx month if liver chemistries stable >/= 4 weeks.

Most patients should have steroid discontinuation by month 3 (keep low dose in immune-mediated liver disease; 5 mg Prednisone a day)

Avoid ISM in:

- Biopsy proven steroid-resistant rejection;
- Etiology is immune mediated disease (initial or re-transplant);
- Previous Antibody Mediated Rejection.

# CNI Monotherapy

If initial 3 post-Tx months were uneventful, try CNI Monotherapy.

TAC trough:

- 0-3 months = 10-15 ng/mL (6 to 8 ng/mL if with MMF for renal sparing)
- 3-6 months = 6-10
- 6-12 months = 5-6
- > 12 months = 3

CSA trough:

- Week 0-2 = 250-350 ng/mL
- Week 3-4 = 200-300
- Week 5-12 = 150-250 (850-1400 2h post)
- 3-6 months = 150-200
- 6-12 months = 100-120
- > 12 months = 90-100

# Dual to Monotherapy Conversion

If patient is on dual therapy after more than 1 year, consider change to monotherapy, if potentially beneficial and low immunological risk.

For renal dysfunction (using MDRD-6 or measured GFR) change to EVL + low dose TAC (</= 5 ng/mL) is better after 1 month and up to year 2.

Target trough level in Monotherapy:

- TAC = 5 ng/mL;
- EVL = 3 to 8 ng/mL +/- MMF 1 gm BID or low dose steroids (higher risk of rejection with EVL monotherapy).

Monitor closely after switch.

# IS in Malignancy

Previous HCC: SRL decreases recurrence in patients within Milan criteria, started 8 weeks after Tx. EVL is being studied.

Previous Non-melanoma skin Cancer: SRL decreases recurrence by 50% (in Kidney Tx).

Post NET and RCC: EVR may be beneficial.

# IS in Renal Dysfunction

Immediately post-LTx: anti-IL2R + MMF induction + delayed TAC or prolonged release TAC until day 5. Then TAC target 6-8 ng/mL + MMF/MPA.

For post-LTx CNI related renal dysfunction with GFR < 60 mL/min/1.73 m2 (CKD 3): after day 28, EVL target 3-8 ng/mL + TAC 3-4 ng/mL.

- Most benefit is obtained with change within the first post LTx year (after day 28).
- Some benefit up to year 2.
- Changes after year 2 do not help.

Triple Therapy Prednisone + CNI + MMF

- Improves patient & graft survival in HCV & Non-HCV.
- Lower ACR rate in HCV & Non-HCV
- Less renal toxicity with lower level of CNI.
- Does not increase risk of infection nor malignancy.

# The Drugs

# Cyclosporin A

From *Tolypocladium inflatum*; approved in 1983. Is calcineurin inhibitor.

Selective immunosuppression by inhibition of T-cell activation.

CyA forms complex with cytoplasmic receptor “cyclophilin” and inhibits calcium- & calmodulin-dependent phosphatase calcineurin.

Inhibition of Ca+ dephosphorilation of NFAT (Nuclear Factor of activated Tcells)

- Calcineurin is vital for the transcriptional process by which IL-2 and other cytokines are activated, which is needed for T-helper cell mediated graft rejection.

# Cyclosporin A

Currently CyA comes as a microemulsion in lipophilic solvent which is less dependent in bile flow (**Neoral, Gengraf**).

CyA is metabolized in the liver by P450-3A pathway.

# Cyclosporin A Toxicity

Nephrotoxicity: can be acute or long term; renal failure in up to 20%; can cause hyperkalemia and hypomagnesemia.

Hyperlipidemia, hyperglycemia, hypertension, gingival hyperplasia, hirsutism.

10-28% may have tremor, peripheral neuropathy, psychoses, hallucinations, motor weakness, or seizures.

May cause Hemolytic Uremic Syndrome.

# Cyclosporin A Dose & Target Levels

Initial 10-15 mg/kg/d divided q 12h; check trough level after 24 h.

New data indicates that level 2-h post dose represents better “total exposure”.

| | |
|---|---|
| Week 0-2: | trough 250-350 ng/mL |
| Week 3-4: | 200-300 |
| Week 5-24: | 150-200<br>(850-1400 2h post) |
| Week 25-52: | 100-120 |
| Thereafter: | 90 - 100 |

# Cyclosporin A + Everolimus (3-8 ng/mL) Goal Trough Levels (Kidney Tx)

- Month 1 post-transplant: 100 to 200 ng/mL
- Months 2 and 3 post-transplant: 75 to 150 ng/mL
- Months 4 and 5 post-transplant: 50 to 100 ng/mL
- Months 6 to 12 post-transplant: 25 to 50 ng/mL

# Cyclosporine A
# Side Effects > 10%

- Cardiovascular: Hypertension (8% to 53%), edema (5% to 14%)
- Central nervous system: Headache (2% to 25%), paresthesia (1% to 11%)
- Dermatologic: Hypertrichosis (5% to 19%)
- Endocrine & metabolic: Hirsutism (21% to 45%), increased serum triglycerides (15%), female genital tract disease (9% to 11%)
- Gastrointestinal: Nausea (2% to 23%), diarrhea (3% to 13%), gingival hyperplasia (2% to 16%), abdominal distress (<1% to 15%), dyspepsia (2% to 12%)
- Genitourinary: Urinary tract infection (kidney transplant: 21%)
- Infection: Increased susceptibility to infection (3% to 25%), viral infection (kidney transplant: 16%)
- Neuromuscular & skeletal: Tremor (7% to 55%), leg cramps (2% to 12%)
- Renal: Increased serum creatinine (16% to ≥50%), renal insufficiency (10% to 38%)
- Respiratory: Upper respiratory tract infection (1% to 14%)

# Cyclosporine A
# Side Effects </= 2%

- Cardiovascular: Chest pain (≤4%), flushing (<1% to 4%), glomerular capillary thrombosis, myocardial infarction
- Central nervous system: Convulsions (1% to 5%), anxiety, confusion, lethargy, tingling sensation
- Dermatologic: Skin infection (7%), acne vulgaris (1% to 6%), nail disease (brittle fingernails), hair breakage, night sweats, pruritus
- Endocrine & metabolic: Gynecomastia (<1% to 4%), hyperglycemia, hypomagnesemia, weight loss
- Gastrointestinal: Vomiting (2% to 10%), anorexia, aphthous stomatitis, constipation, dysphagia, gastritis, hiccups, pancreatitis
- Genitourinary: Hematuria
- Hematologic & oncologic: Leukopenia (<1% to 6%), lymphoma (<1% to 6%), anemia, thrombocytopenia, upper gastrointestinal hemorrhage
- Hepatic: Hepatotoxicity (<1% to 7%)
- Infection: Localized fungal infection (8%), cytomegalovirus disease (5%), septicemia (5%), abscess (4%), fungal infection (systemic: 2%)
- Neuromuscular & skeletal: Arthralgia, myalgia, weakness
- Ophthalmic: Conjunctivitis, visual disturbance
- Otic: Hearing loss, tinnitus
- Respiratory: Sinusitis (<1% to 7%), pneumonia (6%)
- Miscellaneous: Fever

# Drugs that Increase Cyclosporin & Tacrolimus Levels

| **Calcium Channel Blockers** | **Antifungals** | **Macrolide antibiotics** | **Pro-kinetics** | **Miscellaneous** |
|---|---|---|---|---|
| Diltiazem<br>Nicardipine<br>Nifedipine<br>Verapamil | Fluconazole<br>Itraconazole<br>Ketoconazole<br>Voriconazole<br>Clotrimazole | Clarithromycin<br>Erythromycin<br>Troleandomycin<br>Azithromycin<br>Telithromycin | Cisapride<br>Metoclo_pramide | Amiodarone<br>Cimetidine<br>Methyl-prednisolone<br>Omeprazole<br>Protease inhibitors<br>**Nefazodone**<br>**Ethinyl estradiol**<br>**Grapefruit juice** |

# Drugs that Decrease Cyclosporin & Tacrolimus Levels

| **Anticonvulsants** | **Antibiotics** | **Herbal Preparations** | **Miscellaneous** |
|---|---|---|---|
| Carbamazepine<br>Phenobarbital<br>Phenytoin<br>Fosphenytoin | Rifabutin<br>Rifampin<br>Rifapentin | St. John's Wort | **Probucol**<br>**Terbinafine** |

# Tacrolimus

- From *Streptomyces tsukubaensis*.
- It is 100-times stronger than CyA.
- Binds to FKBP12 and the complex inhibits calcineurin; this prevents transcription of IL-2,  IL-3, IL-4, IL-8, and various chemotactic factors.
- It is absorbed in duodenum & jejunum without need for bile.
- Food decrease bioavailability.
- Metabolized via P450-3A pathway.

# Tacrolimus Dose

- **Goal Trough levels**:
  - Monotherapy: 10-15 ng/mL early; 3-6 months = 6-10; 6-12 months = 5-6; > 12 months = 3.
  - If with Everolimus: TAC goal 3 – 4 ng/mL.
- Immediate release (IR):
  - **Prograf**; Initial dose: 0.1 to 0.15 mg/kg/day in 2 divided doses, given every 12 hours
- Extended Release:
  - **Astagraf XL** is not approved for use in liver transplantation due to an increase in mortality in female liver transplant recipients receiving Astagraf XL.
  - **Envarsus PA** [Canadian product]: Initial: 0.11 to 0.13 mg/kg once daily concomitantly used with corticosteroids and/or mycophenolic acids or azathioprine; initiate within 24 hours of transplantation; titrate to target trough concentrations.
    - Conversion from immediate release to extended release: Patients stable on IR tacrolimus converted by initiating ER treatment in a 1:0.7 ratio (1 mg IR:0.7 mg ER) (or a 1:0.85 ratio for African American patients) using previously established total daily dose of IR product. Administer once daily.

# Tacrolimus Toxicity

- More DM than CyA. More HUS than CyA.
- Less HTN, dyslipidemia, hirsutism (TAC causes hair loss), gum hyperplasia than CyA.
- Similar hyperkalemia, tremor, hypomagnesemia, infection, malignancies, & renal dysfunction than CyA.
- Nausea, vomiting, diarrhea, headache.
- Less rejection in 1$^{st}$ year in all, less steroid-resistant rejection, and longer graft survival in Hepatitis C than CyA.

# Tacrolimus

## Side Effects > 10%

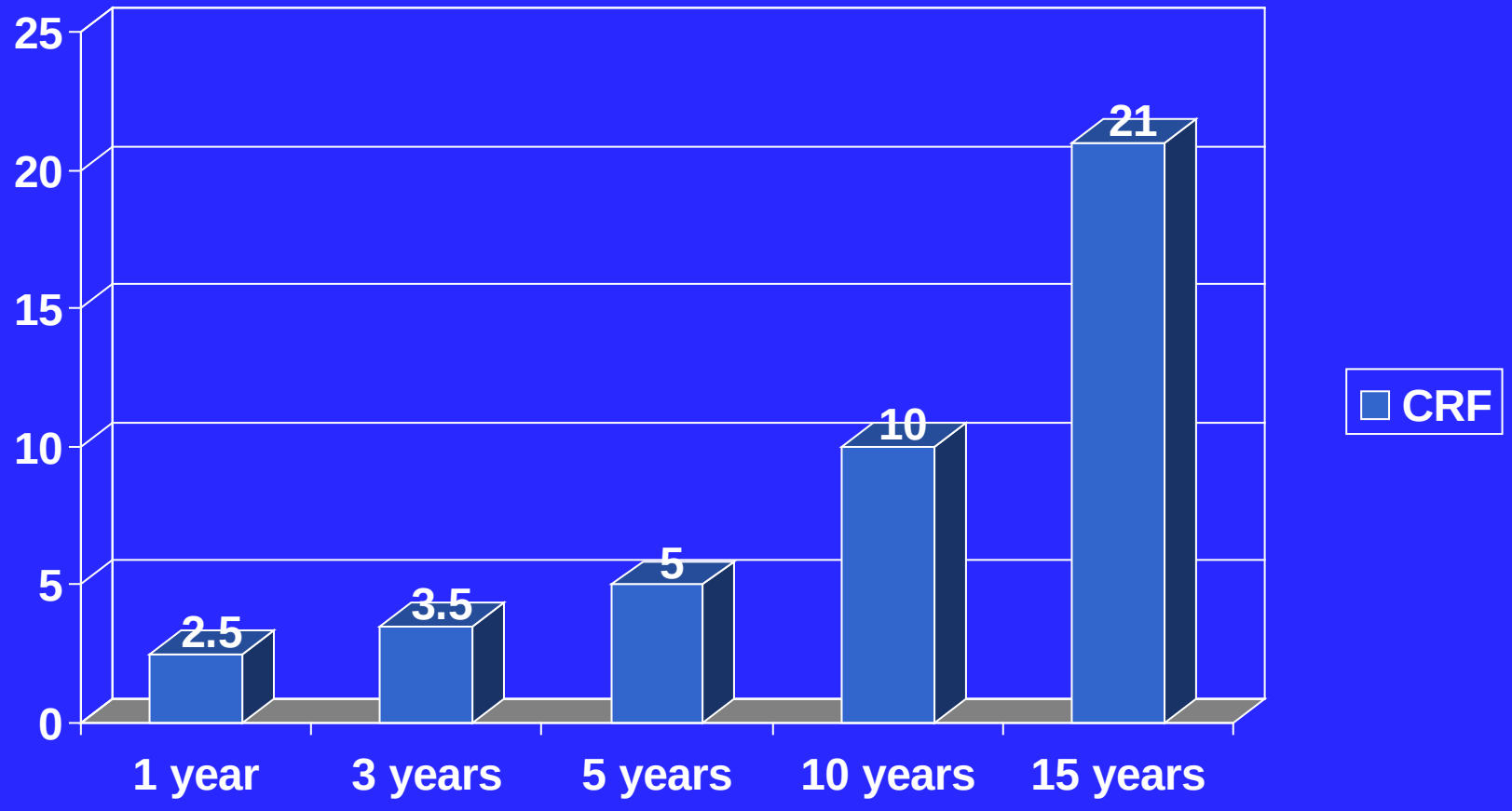
- Cardiovascular: Acute cardiorespiratory failure, angina pectoris, atrial fibrillation, atrial flutter, bradycardia, cardiac arrhythmia, cardiac failure, cardiac fibrillation, chest pain, deep vein thrombophlebitis, deep vein thrombosis, ECG abnormality (including abnormal QRS complex), edema, flushing, hemorrhagic stroke, hypertension, hypotension, orthostatic hypotension, peripheral edema, phlebitis, ST segment changes on ECG, syncope, tachycardia, thrombosis, vasodilation
- Central nervous system: Abnormal dreams, abnormality in thinking, agitation, amnesia, anxiety, ataxia, chills, confusion, depression, dizziness, drowsiness, emotional lability, encephalopathy, falling, fatigue, flaccid paralysis, hallucination, headache, hypertonia, hypoesthesia, insomnia, intolerance to temperature, mobility disorder, mood elevation, myoclonus, nerve compression, nervousness, neuralgia, neuropathy, neurotoxicity, nightmares, pain, paralysis (monoparesis, quadriparesis, quadriplegia), paresthesia, peripheral neuropathy, psychomotor disturbance, psychosis, seizure, vertigo, voice disorder, writing difficulty
- Dermatologic: Acne vulgaris, alopecia, cellulitis, condyloma acuminatum, dermal ulcer, dermatitis, diaphoresis, ecchymoses, exfoliative dermatitis, fungal dermatitis, hyperhidrosis, hypotrichosis, pityriasis versicolor, pruritus, skin discoloration, skin photosensitivity, skin rash
- Endocrine & metabolic: Acidosis, albuminuria, alkalosis, anasarca, cushingoid appearance, Cushing syndrome, decreased serum bicarbonate, decreased serum iron, dehydration, diabetes mellitus (including new-onset), gout, hirsutism, hypercalcemia, hypercholesterolemia, hyperkalemia, hyperlipidemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypervolemia, hypocalcemia, hypoglycemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, increased gamma-glutamyl transferase, increased lactate dehydrogenase, metabolic acidosis, weight gain
- Gastrointestinal: Abdominal distention, abdominal pain, anorexia, aphthous stomatitis, biliary tract disease, cholangitis, cholestasis, constipation, diarrhea, duodenitis, dyspepsia, dysphagia, esophagitis, flatulence, gastritis, gastroenteritis, gastroesophageal reflux disease, gastrointestinal disease, gastrointestinal hemorrhage, gastrointestinal perforation, hernia of abdominal cavity, hiccups, increased appetite, intestinal obstruction, nausea, oral candidiasis, pancreatic pseudocyst, peritonitis, stomatitis, ulcerative esophagitis, vomiting
- Genitourinary: Anuria, bladder spasm, cystitis, dysuria, hematuria, nephrotoxicity, nocturia, oliguria, proteinuria, pyuria, toxic nephrosis, urinary frequency, urinary incontinence, urinary retention, urinary tract infection, urinary urgency, vaginitis

# Tacrolimus

## Side Effects > 10%

- Hematologic & oncologic: Anemia, benign skin neoplasm, decreased platelet count, decreased white blood cell count, disorder of hemostatic components of blood, hemolytic anemia, hemorrhage, hypochromic anemia, hypoproteinemia, hypoprothrombinemia, increased hematocrit, Kaposi sarcoma, leukocytosis, leukopenia, neutropenia, polycythemia, thrombocytopenia, thrombotic microangiopathy
- Hepatic: Abnormal hepatic function tests, ascites, cholestatic jaundice, granulomatous hepatitis, hepatitis (including acute and chronic), hepatotoxicity, hyperbilirubinemia, increased liver enzymes, increased serum alanine aminotransferase, increased serum alkaline phosphatase, increased serum aspartate aminotransferase, jaundice
- Hypersensitivity: Hypersensitivity reaction
- Immunologic: CMV viremia, graft complications
- Infection: Abscess, bacterial infection (may be serious), BK virus (including nephropathy), candidiasis, cytomegalovirus disease, Epstein-Barr infection, herpes simplex infection, herpes zoster infection, infection, opportunistic infection, polyomavirus infection, sepsis (children & adolescents), serious infection
- Neuromuscular & skeletal: Arthralgia, asthenia, back pain, lower limb cramp, muscle cramps, muscle spasm, myalgia, myasthenia, osteoporosis, tremor
- Ophthalmic: Amblyopia, blurred vision, conjunctivitis, visual disturbance
- Otic: Otalgia, otitis media, tinnitus
- Renal: Acute renal failure, hydronephrosis, increased blood urea nitrogen, increased serum creatinine, renal insufficiency, renal failure syndrome, renal tubular necrosis
- Respiratory: Acute respiratory distress syndrome, asthma, atelectasis, bronchitis, decreased lung function, dyspnea, flu-like symptoms, increased cough, nasopharyngitis, pharyngitis, pleural effusion, pneumonia, pneumothorax, productive cough, pulmonary edema, pulmonary emphysema, respiratory tract infection, rhinitis, sinusitis
- Miscellaneous: Abnormal healing, accidental injury, crying, fever, postoperative pain, postoperative wound complication, ulcer, wound healing impairment

# Calcineurin Inhibitors in OLTx
# Risk of Chronic Renal Failure



# Risk Factors for CRF in Non-Renal Tx

| | Relative Risk |
|---|---|
| Post-Op ARF | 2.13 |
| Diabetes Mellitus | 1.42 |
| Age (per each 10 years) | 1.36 |
| Hypertension | 1.18 |
| Hepatitis C | 1.15 |

# Sirolimus/Everolimus

Macrocyclic triene antibiotic with immunosuppressive, antitumor & antifungal properties

Binds to immunophilin FKBP12 but has different action than TAC: blocks cell-cycle progression at the “G1 – S phase” junction; mTOR.

No calcineurin inhibition, hence no increase in endothelin nor TGF beta that cause vasoconstriction and renal injury.

Suppresses cytokine driven T Cell proliferation.

Increase risk of Hepatic Artery Thrombosis: “The safety and efficacy of Sirolimus…has not been established in liver transplant patients, and therefore such use is not recommended”.

# Properties of mTOR inhibitors

- Synergism
- Anti-tumor effect (Kaposi, RCC, HCC).
- Vascular
- Potent inhibitor of proliferation.
- Anti fibrotic (TGFbeta)
- Tolerance (Tregs)

Sirolimus/Everolimus
Toxicity
& Dose

Anemia, hypercholesterolemia, hypertrigliceridemia, hyperlipidemia, leukopenia, thrombocytopenia, interstitial lung disease, peripheral edema, wound dehiscence, lymphocele, oral ulcers.

Dose Sirolimus: 2 mg/d, adjusted to maintain trough level of 4-10 ng/mL.

Everolimus given BID due to short half-life.

# Sirolimus

- Macrolide antibiotic produced by Streptomyces hygroscopicus.
- Structurally similar to tacrolimus and binds the same target (FK-binding protein) but does not inhibit calcineurin.
- Blocks the transduction signal from the IL-2 receptor, thus inhibiting T- and B-cell proliferation.
- Its advantage over the calcineurin inhibitors (CNIs) is its freedom from nephrotoxicity and neurotoxicity.
- Side effects of sirolimus have relegated it to the status of an important **second-line drug**.

# Everolimus
# Zortress

- Derivate of Sirolimus and works as an mTOR inhibitor.
- Initial Dose: 1 mg twice daily (q12 h) (in combination with reduced dose tacrolimus and a corticosteroid;
- Trough Goal: 3 – 8 ng/mL with reduced dose TAC (TAC goal of 3-4 ng/mL); EVL monotherapy goal is 6 – 10 ng/mL), but usually not recommended,
- Adjust maintenance dose if needed at a 4- to 5-day interval (from prior dose adjustment) based on serum concentrations tolerability, and response.
- Avoid concomitant administration of P-gp and strong CYP3A4 inhibitors.
  - If trough is <3 ng/mL: Double total daily dose (using available tablet strengths).
  - If trough >8 ng/mL on 2 consecutive measures: Decrease dose by 0.25 mg twice daily.

# Everolimus
# Side Effects > 10%

- **CV**: Peripheral edema (liver transplant: 18% to 20%), hypertension (17% to 30%);
- **CNS**: Headache (18% to 22%), insomnia (liver transplant: 6% to 7%), procedural pain (kidney transplant: 15%), fatigue (9% to 11%);
- **Endo**: Diabetes mellitus (new onset: liver transplant: 32%), hyperkalemia (renal transplant: 18%), hypercholesterolemia (9% to 17%), hypomagnesemia (kidney transplant: 14%), hypophosphatemia (kidney transplant: 13%), hyperglycemia (kidney transplant: 12%), hypokalemia (kidney transplant: 12%);
- **GI**: Constipation (kidney transplant: 38%), nausea (liver transplant: 14% to 15%), diarrhea (19% to 24%), vomiting (kidney transplant: 15%), abdominal pain (13% to 15%);
- **GU**: Urinary tract infection (kidney transplant: 22%), hematuria (kidney transplant: 12%), dysuria (kidney transplant: 11%);
- **Hem**: Anemia (kidney transplant: 26%), leukopenia (3% to 13%);
- **Infection**: Infection (liver transplant: 50%), viral infection (liver transplant: 17%), bacterial infection (liver transplant: 16%), hepatitis C (liver transplant: 11% to 14%);
- **Neuro, M-S**: Limb pain (kidney transplant: 12%), back pain (kidney transplant: 11%);
- **Renal**: Increased serum creatinine (kidney transplant: 18%);
- **Resp**: Upper respiratory tract infection (kidney transplant: 16%);
- **Miscellaneous**: Postoperative wound complication (liver transplant: 11%; includes incisional hernia, lymphocele, seroma, wound dehiscence), fever (13% to 19%)

# Everolimus
# Side Effects 1-10%

- **CV**: Chest pain (5%), tachycardia (3%), cardiac failure (1%), deep vein thrombosis (<1%)
- **CNS**: Depression (5%), paresthesia (5%), chills (4%), aggressive behavior (≤2%)
- **Derm**: Alopecia (10%), palmar-plantar erythrodysesthesia (5%), erythema (4%), onychoclasis (4%), skin lesion (4%), acneiform eruption (3%)
- Endo: Diabetes mellitus (10%; new onset: <1%), heavy menstrual bleeding (6% to 10%), menstrual disease (6% to 10%), decreased serum fibrinogen (8%), increased luteinizing hormone (1% to 4%), increased follicle-stimulating hormone (3%), ovarian cyst (≤3%), exacerbation of diabetes mellitus (2%)
- **GI**: Gastroenteritis (10%), hemorrhoids (5%), dysphagia (4%)
- **GU**: Vaginal hemorrhage (8%), dysmenorrhea (6%), uterine hemorrhage (6%), cystitis (3%), proteinuria (2%)
- **Hem/Onc**: Hemorrhage (3%)
- **Hepatic**: Increased serum bilirubin (3%)
- **Hypersensitivity**: Hypersensitivity reaction (≤3%; includes anaphylaxis, chest pain, dyspnea, flushing), angioedema (≤1%)
- **Infection**: Candidiasis (<1%), hepatitis C (<1%), sepsis (<1%)
- **M-S**: Muscle spasm (10%), jaw pain (3%)
- **Ophthalmic**: Eyelid edema (4%), conjunctivitis (2%)
- **Otic**: Otitis media (6%)
- **Renal**: Renal failure syndrome (3%)
- **Respiratory**: Streptococcal pharyngitis (10%), pleural effusion (7%), pneumonia (2% to 6%), bronchitis (4%), pharyngolaryngeal pain (4%), rhinorrhea (3%), sinusitis (3%)
- **Miscellaneous**: Postoperative wound complication (<1%; wound healing impairment)

# Drugs that Increase Sirolimus or Everolimus Concentration

| **Calcium Channel Blockers** | **Antifungals** | **Macrolide antibiotics** | **Pro-kinetics** | **Miscellaneous** |
|---|---|---|---|---|
| Diltiazem<br>Nicardipine<br>Nifedipine<br>Verapamil | Fluconazole<br>Itraconazole<br>Ketoconazole<br>Voriconazole<br>Clotrimazole | Clarithromycin<br>Erythromycin<br>Troleandomycin<br>Azithromycin<br>Telithromycin | Cisapride<br>Metoclo_pramide | Amiodarone<br>Cimetidine<br>Omeprazole<br>Methyl-prednisolone<br>Protease inhibitors<br>**CyA**<br>**Graprfruit juice** |

# Drugs that Decrease Sirolimus or Everolimus Concentration

| **Anticonvulsants** | **Antibiotics** | **Herbal Preparations** |
|---|---|---|
| Carbamazepine<br>Phenobarbital<br>Phenytoin<br>Fosphenytoin | Rifabutin<br>Rifampin<br>Rifapentin | St. John’s Wort |

# Special Conditions to use Sirolimus/Everolimus

| | |
|---|---|
| HCC | Anti-tumor Effect |
| HCV & PSC | Anti-fibrotic Effect |
| Renal Insufficiency | Spares CNI |

# Corticosteroids

- Block T-cell-derived and antigen-presenting cell-derived cytokine expression, decreasing IL-1, IL-2, IL-3, and IL-6
- Are used in reversing acute rejection and in maintenance.
- **Side effects**: hypertension, mental status changes, dyslipidemia, poor wound healing, hyperglycemia, gastric ulcers, myopathy, osteoporosis, Cushing S., fungal/bacterial infections, pituitary axis suppression, fluid retention, cataracts.
- Dose: 500-1000 mg pre-op; then taper from 50 to minimal dose over a few months.

# Beneficial Effect of Steroid-Withdrawal after 3 months post OLTx

| | Steroids | No-Steroids | P-value |
|---|---|---|---|
| Hypertension | 58 % | 15 % | 0.0002 |
| Diabetes | 25 % | 6 % | 0.007 |
| Infection | 17 % | 2 % | 0.05 |
| Bone Disease | 9 % | 0 % | 0.05 |
| Mean Cholesterol | 253 mg/dL | 183 mg/dL | 0.001 |

# Adverse Effects of Steroid-Withdrawal

- Recurrent AIH & PBC
- Worsens HCV if done before 3rd month.
- Flare up of Ulcerative Colitis
- Arthralgias
- Depression

# Azathioprine (AZA)

Antimetabolite; antagonises purine metabolism. Inhibits synthesis of DNA, RNA, and proteins.

Used in < 5% US transplant centers.

Can cause myelosuppression and hepatotoxicity.

**Side effects**: nausea, vomiting, diarrhea, pancreatitis, anemia, leukopenia, thrombocytopenia, and weight loss.

Usual dose: 1-2 mg/kg/d

# Mycophenolate Mofetil (MMF) Mycophenolic Acid (MPA)

Inhibit de novo purine nucleotide synthesis by abrogation of inosine monophosphate dehydrogenase and production of guanosine nucleotides.

Blocks DNA replication in T & B lymphocytes which are unable to use alternate salvage pathways.

Liver dysfunction increase half life by decreasing conjugation; albumin levels change pharmacokinetics.

More than 50% on transplant programs use them.

Dose reduction and withdrawal are needed in 24-57%.

# MMF & MPA Toxicity & Dose

Nausea, vomiting, abdominal pain, diarrhea, anemia, leukopenia, thrombocytopenia, hypercholesterolemia, hypokalemia, tremor, hypertension, edema.

MMF: 2-3 g/day, divide q 12h

MPA: 720-1440 mg/d divided q 12h.

# MMF and MPA Toxicity

## Side Effects > 10%

- **CV**: Hypertension (18% to 79%), edema (17% to 68%), hypotension (34%), tachycardia (22% to 23%), lower extremity edema (16%)
- **CNS**: Pain (25% to 79%), headache (11% to 59%), insomnia (24% to 52%), dizziness (34%), depression (20%), chills (3% to <20%), confusion (3% to <20%), drowsiness (3% to <20%), hypertonia (3% to <20%), malaise (3% to <20%), myasthenia (3% to <20%), paresthesia (3% to <20%)
- **Derm**: Skin rash (26%), ecchymoses (20%), cellulitis (3% to <20%)
- **Endo**: Hyperglycemia (44% to 48%), hypercholesterolemia (46%), hypomagnesemia (20% to 39%), hypokalemia (9% to 37%), hypocalcemia (11% to 30%), increased lactate dehydrogenase (24%), hyperkalemia (22%), acidosis (3% to <20%), weight loss (3% to <20%), hyperuricemia (13%), hyperlipidemia (10% to 12%), hypophosphatemia (9% to 11%)
- **GI**: Abdominal pain (22% to 63%), nausea (27% to 56%), diarrhea (24% to 53%), constipation (38% to 44%), vomiting (20% to 39%), decreased appetite (25%), dyspepsia (19% to 23%), esophagitis (3% to <20%), gastric ulcer (3% to <20%), gastritis (3% to <20%), gastrointestinal hemorrhage (3% to <20%), hernia of abdominal cavity (3% to <20%), intestinal obstruction (3% to <20%), stomatitis (3% to <20%), upper abdominal pain (14%), flatulence (10% to 13%)
- **GU**: Urinary tract infection (29% to 33%), hematuria (3% to <20%)
- **Hem/Onc**: Leukopenia (19% to 46%), anemia (20% to 45%), leukocytosis (22% to 43%), thrombocytopenia (24% to 38%), benign skin neoplasm (3% to <20%), disorder of hemostatic components of blood (3% to <20%), neoplasm (3% to <20%), pancytopenia (3% to <20%), skin carcinoma (3% to <20%; non-melanoma: 1% to 12%)
- **Hepatic**: Increased liver enzymes (25%), hepatitis (3% to <20%), increased serum alkaline phosphatase (3% to <20%)
- **Infection**: Bacterial infection (27% to 40%), viral infection (31%), cytomegalovirus disease (4% to 22%), fungal infection (11% to 12%)
- **M-S**: Asthenia (35% to 49%), tremor (12% to 34%), back pain (6% to 12%), arthralgia (7% to 11%)
- **Renal**: Increased serum creatinine (10% to 42%), increased blood urea nitrogen (37%)
- **Respiratory**: Dyspnea (31% to 44%), cough (41%), pleural effusion (34%)
- **Miscellaneous**: Fever (13% to 56%)

# MMF and MPA Toxicity

## Side Effects 1 - 10%

- **CV**: Exacerbation of hypertension (<10%), peripheral edema (<10%), phlebitis (4%), thrombosis (4%)
- **CNS**: Anxiety (<10%), fatigue (<10%)
- **Derm**: Acne vulgaris (<10%), pruritus (<10%)
- **Endo**: Diabetes mellitus (<10%)
- **GI**: Abdominal distension (<10%), gastroesophageal reflux disease (<10%), gingival hyperplasia (<10%), oral candidiasis (<10%)
- **GU**: Urinary retention (<10%)
- **Hem/Onc**: Lymphocele (<10%), severe neutropenia (2% to 4%), malignant neoplasm (≤2%), malignant lymphoma (1%), lymphoproliferative disorder (≤1%)
- **Hepatic**: Abnormal hepatic function tests (<10%)
- **Infection**: Influenza (<10%), wound infection (<10%), herpes simplex infection (6% to 8%), herpes zoster infection (4% to 5%), sepsis (2% to 5%)
- **M-S**: Muscle cramps (<10%), myalgia (<10%), peripheral pain (<10%)
- **Ophthalmic**: Blurred vision (<10%)
- **Renal**: Renal insufficiency (<10%), renal tubular necrosis (<10%)
- **Respiratory**: Dyspnea on exertion (<10%), nasopharyngitis (<10%), pneumonia (<10%), sinusitis (<10%), upper respiratory tract infection (<10%)

# Drug-Drug Interaction
# Azathioprine & Mycophenolate

| **Increases AZA** | **Increases MMF** | **Decreases AZA & MMF** |
|---|---|---|
| Allopurinol | Probenecid | Cholestiramine |
| Methotrexate | Tacrolimus | Antacids |
| ACE inhibitors | | Iron preparations |

# Antithymocyte Globulin (ATG)

ATGAM (equine) and Thymoglobulin (rabbit)

Polyclonal Ab against T-cells epitopes (CD2, CD3, CD4, CD8, CD28, & T-cell receptor), NK cells epitopes (CD16), and macrophages.

Cause T-cell depletion by: apoptosis, antibody mediated cytolysis, and internalization of cell surface receptors.

First dose can cause “cytokine release S”: fever, chills, tachycardia, chest pain, bronchospasm, GI disturbances, blood pressure changes. Steroids + Benadryl + acetaminophen helps.

Used in 6% of US transplant programs.

Dose: 1.5-5 mg/kg/d over 4-6 h infusion, for 3-5 days.

# Muramonab-CD3 (OKT3)

Murine Ab against T-cell CD3 antigen; inactivates T-cell receptor.

Cytokine release syndrome is very common 1-3 h after first dose. Sometimes life-threatening with pulmonary edema and shock.

Re-exposure to OKT3 may decrease efficacy.

Dose: 5 mg IV q day x 10-14 days for steroid resistant rejection.

# IL-2 receptor antibodies Basiliximab & Daclizumab

Basiliximab (Simulect) is chimeric, Daclizumab (Zenapax) is humanized;

Bind to IL-2R alpha-chain present in activated T-lymphocytes. Causes competitive antagonism of IL-2 induced T-cell proliferation.

Effect up to **3 weeks with Basiliximab**, and **10 weeks with Daclizumab**.

Side effects are mild.

Dose:

- a) Basiliximab: 20 mg IV pre-op + 20 mg 4 d later.
- b) Daclizumab: 1 mg/kg every 14 days x 5 doses.

# Liver Transplant Rejection

# Immune System

**Immune system:**

- protects against infectious invasion, and
- provides self-nonself discrimination.

**It has two sub-systems:**

- Rapid response: done by innate immunity system.
- Specific response: classic T-cell response requiring days to weeks; this T-cells mediate graft rejection but also tolerance.

**Both sub-systems are coordinated and provide immunological memory.**

# Hyperacute Rejection

- Extremely rare.
- Occurs hours to days after transplantation,
- Target is vascular endothelium.
- Antibody-mediated, & complement dependent graft destruction by ***coagulative necrosis***.
- Preformed antibodies specific to MHC.
- Lack of lymphocytic infiltration.

# Acute T-Cell Mediated Rejection

Occurs in 45-70% of patients.

Days to months after transplant (usually initial 3 months).

Classical, cell-mediated rejection:

- Predominantly CD4 & CD8 T-cells.
- Directed against donor MHC antigens (cholangiocytes & vascular endothelium)

Target of current immunosuppression.

Diagnostic Triad:

- Portal inflammation
- Bile-duct damage
- Venular endothelium inflammation.

# Banff Rejection Activity Index

| Category | Criteria | Score |
|---|---|---|
| Portal Inflammation | Mostly lymphocytic inflammation involving, but not noticeably expanding, a minority of the triads | 1 |
| | Expansion of most or all of the triads, by a mixed infiltrate containing lymphocytes with occasional blasts, neutrophils and eosinophils | 2 |
| | Marked expansion of most or all of the triads by a mixed infiltrate containing numerous blasts and eosinophils with inflammatory spillover into the periportal parenchyma | 3 |
| Bile Duct Inflammation Damage | A minority of the ducts are cuffed and infiltrated by inflammatory cells and show only mild reactive changes such as increased nuclear:cytoplasmic ratio of the epithelial cells | 1 |
| | Most or all of the ducts infiltrated by inflammatory cells. More than an occasional duct shows degenerative changes such as nuclear pleomorphism, disordered polarity and cytoplasmic vacuolization of the epithelium | 2 |
| | As above for 2, with most or all of the ducts showing degenerative changes or focal lumenal disruption | 3 |
| Venous Endothelial Inflammation | Subendothelial lymphocytic infiltration involving some, but not a majority of the portal and/or hepatic venules | 1 |
| | Subendothelial infiltration involving most or all of the portal and/or hepatic venules | 2 |
| | As above for 2, with moderate or severe perivenular inflammation that extends into the perivenular parenchyma and is associated with perivenular hepatocyte necrosis | 3 |

Mild = up to 3; Moderate = 4 to 6; Severe = 7 or more

# Acute T-Cell Mediated Rejection (TCMR)

**Generally 5-30 days; 10-20% of patients.**

- Early in initial 90 days;
- Late after 90 days (7.5 to 23% of patients); decreases graft survival.

**Higher in: Autoimmune dz, females, young age, DR mismatch, re-transplant.**

**Usually asymptomatic unless late diagnosis.**

- Fever, Abdominal pain, Ascites, Leukocytosis, Eosinophilia

**Biochemical abnormalities not specific (high GGT)**

**Diagnosis require liver Bx.**

- Repeat Liver Bx if suboptimal biochemical response. No biopsy needed with good biochemical response.

# Management of Acute T-Cell Mediated Rejection

Moderate to Severe: Corticosteroids.

Refractory:

- ATG;
- Consider Antibody Mediated Rejection (C4D staining + Donor Specific AB testing).

Investigate the reason of rejection.

Optimize immunosuppression.

If already optimized, add MMF, AZA or SRL.

Consider long term prednisone in:

- autoimmune liver dz, or
- after 2 episodes of severe AR.

# Treatment of Acute TCMR

| Severity of Acute TCMR | Treatment |
|---|---|
| Mild Acute TCMR | Increase CNI level + /- add anti-metabolity (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-metabolity (mycophenolate) or mTORi<br>Anti-infection Prophylaxis x **3 months**<br>Valgancyclovir 900 mg/d + Bactrim 160/800 mg/d<br>or Atavaquone 1500 mg/d + Fluconazole 400 mg/d |
| Failure to Respond or Severe Cholestatic TCMR | Anti-thymocyte globulin<br>Anti-infection Prophylaxis x **6 months**<br>Valgancyclovir 900 mg/d + Bactrim 160/800 mg/d<br>or Atavaquone 1500 mg/d + Fluconazole 400 mg/d |

# Variants of Classic Acute TCMR

**Plasma cell hepatitis:**

- Early, often with (-) auto-Abs (> 60%)
- Centrilobular necrosis
- ? Antibody mediated Rejection

**Idiopathic post-transplantation hepatitis:**

- 5-15% with fibrosis progressing to cirrhosis over 10 y.
- Auto-Abs and plasma cell are associated with progression.

**Late Acute Rejection (> 6 months after LT):**

- May be histologically different.
- Lobular activity, interface hepatitis, central perivenulitis (without endothelitis); can mimic plasma cell hepatitis.
- Possible evolution to chronic rejection with perivenular hepatocyte drop out and loss of inflammation.

# Antibody Mediated Rejection When to Consider

## RISK FACTORS:

- Refractory Rejection (steroid resistant).
- Re-transplant (sensitized).
- HLA mismatch, positive x-match.
- Necrosis or vascular injury.

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

## PROPHYLAXIS:

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

# 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.

# 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.

# Lesion Scoring of AMR
## C4d-(immune)-score (formalin-fixed, paraffin-embedded) (C4d Score)

- 0. No C4d deposition in portal microvasculature
- 1. Minimal (<10% portal tracts) C4d deposition in >50% of the circumference of portal microvascular endothelia (portal veins and capillaries)
- 2. Focal (10–50% portal tracts) C4d deposition in >50% of the circumference of portal microvascular endothelia (portal veins and capillaries)—usually without extension into periportal sinusoids
- 3. Diffuse (>50% portal tracts) C4d deposition in >50% of the circumference of portal microvascular endothelia (portal veins and capillaries)—often with extension into inlet venules or periportal sinusoids

# Lesion Scoring of AMR Histology Score (h-score)

- 1. Portal microvascular endothelial cell enlargement (portal veins, capillaries, and inlet venules) involving a majority of portal tracts with sparse microvasculitis defined as three to four marginated and/or intraluminal monocytes, neutrophils, or eosinophils in the maximally involved capillary with generally mild dilation.
- 2. Monocytic, eosinophilic, or neutrophilic microvasculitis/capillaritis, defined as at least 5–10 leukocytes marginated and/or intraluminal in the maximally involved capillary prominent portal and/or sinusoidal microvascular endothelial cell enlargement involving a majority of portal tracts or sinusoids, with variable but noticeable portal capillary and inlet venule dilatation and variable portal edema.
- 3. As above, with marked capillary dilatation, marked microvascular inflammation (10 or more marginated and/or intraluminal leukocytes in the most severely affected vessels), at least focal microvascular disruption with fibrin deposition, and extravasation of red blood cells into the portal stroma and/or space of Disse (subsinusoidal space).

# Acute Antibody Mediated Rejection

- **Definite for acute/active AMR (all four criteria required):**
  - Histopathological pattern of injury consistent with acute AMR, usually including the following:
    - portal microvascular endothelial cell hypertrophy, portal capillary and inlet venule dilatation, monocytic, eosinophilic, and neutrophilic portal microvasculitis, portal edema, ductular reaction;
    - cholestasis is usually present, but variable;
    - edema and periportal hepatocyte necrosis are more common/prominent in ABO-incompatible allografts;
    - variable active lymphocytic and/or necrotizing arteritis
  - Positive serum DSA (Mean Fluorescent Intensity >/= 5000).
  - Diffuse (C4d score = 3)
    - microvascular C4d deposition on frozen or formalin-fixed, paraffin-embedded tissue in ABO-compatible tissues or
    - portal stromal C4d deposition in ABO-incompatible allografts.
  - Reasonable exclusion of other insults that might cause a similar pattern of injury. Most cases will score (C4d-score: 3+ h-score = 5 or 6).

# Acute Antibody Mediated Rejection

## Suspicious for AMR (both criteria required):

- DSA is positive (Mean Fluorescent Intensity >/= 5000).
- Non-zero h-score with: C4d-score + h-score of 3 or 4.

## Indeterminate for AMR (requires 1+2 and 3 or 4):

- 1. C4d-score + h-score is ≥ 2.
- 2. DSA not available, equivocal, or negative.
- 3. C4d staining not available, equivocal, or negative.
- 4. Co-existing insult might be contributing to the injury.

# Chronic AMR

## Probable chronic active AMR (all four criteria are required):

- Histopathological pattern of injury consistent with chronic AMR; both required:
  - Otherwise unexplained and at least mild mononuclear portal and/or perivenular inflammation with interface and/or perivenular necro-inflammatory activity.
  - At least moderate portal/periportal, sinusoidal and/or perivenular fibrosis.
- Recent (for example, measured within 3 months of biopsy) circulating HLA DSA in serum samples;
- At least focal C4d-positive (>10% portal tract microvascular endothelia.
- Reasonable exclusion of other insults that might cause a similar pattern of injury.

## Possible chronic active AMR:

- As above, but C4d staining is minimal or absent

# GVHD post Liver Transplant

Less than 1%, but > 80% mortality.

Usually 2-8 weeks post-LT

TRIAD: Skin Rash + Cytopenia + Diarrhea, with normal Liver Enzymes and allograft function.

Diagnosis: FISH X-Y chimerism, PBMC donor-recipient chimerism, skin Bx, or rarely intestinal Bx.

Treatment:

- High dose steroids
- ? Lymphodepletion
- ? Stop immunosuppression
- Stem Cell transplant.

# The Immune System and Liver Transplantation

# T-cell Recognition of Alloantigen & T-cell Activation: Rejection

Recipient T-lymphocytes recognize a donor alloantigen by:

- a) ***Direct Path*** : native donor ***MHC*** molecule expressed ***in donor APCs*** **,**
- b) ***Indirect Path*** : ***donor alloantigen peptides*** (from damaged cells or soluble MHC class I) ***presented by recipient APCs***.

"Direct path" dominates in "acute" rejection, and

"Indirect path" in chronic rejection and tolerance.

# Costimulatory Pathways & Transplantation: Rejection

Optimal T-lymphocyte activation need TWO coordinated signals:

- **Signal 1**: T-cell Receptor (TCR) signal, which occurs after recognition of peptide/MHC on APC, (blocked by TAC, CyA, OKT3, Thymoglobulin, ALG, Alemtuzumab (CD52))
- **Signal 2**: occurs from interaction of "costimulatory T-cell molecule" with its "ligand" on the APC (blocked by CTLA4Ig, CD40L, CD28/B7, CD40/CD154)

If signal 1 & 2 occur, rejection develops.

- **Signal 3:** is blocked by IL2 receptor Monoclonal Ab, Rapamycin, AZA & MMF)

# Effector Pathways of Graft Injury Rejection

There is not a single mediator or cell type that is absolutely required for allograft rejection; there are several redundant and compensatory mechanisms contributing to rejection.

After [T-cell Receptor signal + costimulatory signal, + cytokines], there is proliferation and maturation of $CD4^+$ or $CD8^+$ T-cells capable of graft injury; this will lead to:

- T-cell mediated cytotoxicity
- Delayed hypersensitivity
- Antibody-mediated damage

# Effector Pathways of Graft Injury Rejection

- **<u>T-cell mediated cytotoxicity</u>**:
  - ***A) CD8+*** cytotoxic T-lymphocytes (CTLs) specific for donor ***class I***, cause apoptosis through biochemical mechanisms (perforin/granzyme B in a $Ca^{++}$ dependent process, and Fas/FasL through caspase 8);
  - ***B) NK cells***, ***without*** need for ***activation*** or sensitization, which can cause apoptosis through FasL & granzyme B.

# Effector Pathways of Graft Injury Rejection

- **<u>Delayed hypersensitivity</u>**:
  - ***CD4*⁺** T-lymphocytes specific for donor ***class II***, release IFN gamma activating macrophages and cellular mediators.
- **<u>Antibody-mediated damage</u>**:
  - Antibodies against liver sinusoidal endothelial cells (LSECs) indirectly promote acute rejection.

# Immune System & Tolerance

- **Tolerance**: Absence of destructive response to an allograft in immunocompetent host.
- Tolerance is accomplished by T-cell suppression mediated by :
  - a) **cell-contact dependent mechanism**: $CD4^+CD25^+$ cells,
  - b) **cytokine mediated T-cell mechanism**: T regulatory-1 & T helper-3 (Th3),
  - c) **antigen presentation dependent mechanism**: by liver-derived Dendritic Cells (DCs) and by Liver Sinusoidal Endothelial Cells (LSECs) which behave as immature DCs causing incomplete activation, inhibiting T-cell response.
  - d) **NK cells** which give a “death signal” to recipient derived T-cell passing through the graft.

# Costimulatory Pathways & Transplantation: Tolerance

- Optimal T-lymphocyte activation needs coordinated “signal-1” and “signal-2” stimuli.
- If only “signal 1” occurs, tolerance develops;
- To prevent rejection and induce tolerance, you can disrupt “signal 2”:
  - a) CTLA4 (cytotoxic T lymphocyte antigen 4) can compete with CD28 for B7, and gives “negative costimulation”; CTLA4-Ig fusion protein has been used for this goal,
  - b) anti-CD154 disrupts CD40/CD154 pathway.
- Programmed death-1 (PD-1) is a molecule induced upon T-cell activation and causes a “negative signal” similar to CTLA4, causing spontaneous tolerance.
  - PD-1 binds to ligands PDL-1 & PDL-2.

# Possible Mechanisms for Liver Tolerance

- 1) The liver produces large amounts of soluble MHC class I antigen, causing:
  - a) Passive blockade of alloantibodies & donor-specific effectors, or
  - b) Activation-induced apoptosis of allospecific CTLs.
- 2) Liver suppressor factor-1: is produced by spontaneously tolerant recipients and prolongs rat cardiac allograft survival.
- 3) Liver produces a soluble Fas “incomplete variant”, which inhibits anti-Fas induced apoptosis and inhibits CTL function in vitro.

# Possible Mechanisms for Liver Tolerance

- 4) Graft-derived Stem-cells migrate out of the liver and establish “microchimerism” with clonal exhaustion/deletion of host alloreactive T-cells.
- 5) Inmature “Dendritic Cells” (DCs) and “Liver Sinusoidal Endothelial Cells” (LSECs) do not express enough costimulatory molecules, hence facilitate tolerance.
- 6) Kupffer cells (APCs) express FasL which can induce apoptosis of host T-cells.

# Costimulatory Pathways & Transplantation: Autoimmunity

- Deficiency in “Programmed death-1” (PD-1) molecule and/or PDL-1 causes autoimmune disorders and autoimmune hepatitis with large amounts of CD8 T-cells in the liver.

# Steroid Avoidance

**Reason**: Minimize osteoporosis, hyperglycemia, hypertension, hyperlipidemia, infections, Cushingoid features, and HCV recurrence.

**TAC+MMF+Thymoglobulin vs. TAC+MMF+Steroids**:

- F/U 1.5 y, graft survival 89% in both, rejection (20 vs 32%, $p<0.05$), recurrent HCV (50 vs 71%, p=ns)

**TAC+daclizumab vs TAC+Steroids**:

- F/U 3 months, daclizumab group had less steroid resistant rejection, DM, and CMV infection

***Larger randomized studies with longer F/U are needed.***

# Renal Sparing Protocols

Up to 21% of LTx patients develop CRF within 5 years.

18% of patients have ***severe*** renal dysfunction after 13 years.

Adding MMF and reducing dose of calcineurin inhibitor (CNI) can improve GFR by 15% in 50% of patients even if done > 1 y post-OLTx; if CNI is D/C, rejection risk is increased.

# Conversion from CNI to Sirolimus

28 patients with creatinine > 1.8 mg/dL were converted; mean time= 2y post-LTx.

Dose: 2 mg/d, titrated to 4-10 ng/mL.

14 (50%) had improvement in GFR;
7 progressed to ESRD, and
6 did not tolerate the change.

Large randomized trials are ongoing to evaluate proper time to change.