Immunosuppressive Agents in Liver Transplantation

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Discovery of Immunosuppressants

XRT ANTI-T CELL Abs CYCLOSPORINE TACROLIMUS MMF RAPA BREGUNAN LEFLUNAMIDE CTLA-4Ig IL2-Ras FTY 720/KRP203 Alemtuzumab Belatacept Efalizumab Everolimus Rituximab ISA 247 AE5071 CP-690550


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"BOY! TALK ABOUT ORGAN REJECTION!"
Optimizing Immunosuppression

- Individualization
  - Based on expected or existing drug toxicities
  - Choose agents for specific disease states after OLT

- Minimization
  - Use less over time to reduce side effects

Rationale For Individualizing Immunosuppression

**Too Much**
- Cardiovascular Disease
- Infection
- Neoplasia
- Nephrotoxicity
- Neurotoxicity
- Non compliance!!!!

**Too Little**
- Allograft Rejection
- Allograft loss
Tacrolimus (FK-506, Prograf®)

- Most common immunosuppressive agent used in OLT
- 10-100 times more potent than cyclosporine

Rationale for Use in OLT

Tacrolimus

- Corticosteroid sparing
- Reduces frequency and severity of acute rejection episodes
- Effective as Rescue therapy
  - chronic rejection in OLT
- Increases patient/graft survival
- Pediatric advantages

Pharmacokinetics/Interactions

Tacrolimus

- Absorption: variable absorption from the small bowel
- Elimination: removed from the body by the liver
- Tacrolimus is not dialyzable
- Many drug interactions with prescription and non prescription drugs
  - Patients need to avoid adding any medications, herbs, supplements following OLT
Tacrolimus

**Dose and Monitoring**

**Oral Dose**
- adults: 0.1mg/kg/d*
- peds: 0.15mg/kg/d
- elderly (>60yrs): reduce dosage
- IV form usually not required
- availability: 0.5, 1mg and 5mg capsules
- No suspension commercially available
- SL occasionally used

**Monitoring (OLT)**

<table>
<thead>
<tr>
<th>Trough level:</th>
<th>Level*: Days Post Tx</th>
<th>Level*: (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-30</td>
<td>5-8</td>
<td></td>
</tr>
</tbody>
</table>

*varies based on immune complications, disease state, ADRs

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**Adverse Effects**

- Nephrotoxicity
  - Acute, chronic (avoid motrin like drugs)
- Neurotoxicity - tremor, headache, memory problems, seizure, CPM, PRES, etc
- Gastrointestinal intolerance (nausea, diarrhea)
- Hyperglycemia (worse than CSA)
- Electrolyte disturbances - hyperkalemia, hypomagnesemia
- Other: alopecia, PTLD (higher incidence in pediatric)
- Risk of infections and cancers

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**Summary**

- Potent and effective immunosuppressant
- Relatively well tolerated
- Used initially in liver transplantation
  - First choice in virtually all SOT populations
  - Many Generic formulations are available
  - Sustained release forms are here!
Mycophenolate mofetil (Cellcept®)

- Clinical use in liver transplant recipients (with tacrolimus and steroids) for prevention of rejection
- Mycophenolic acid enteric coated (Myfortic) also available
- Many Generic forms are available

Dose and Administration

Mycophenolate

- Initial dose should be given within 24 hours of transplant
- Cellcept: 1.0 g given bid (2 g/day) in combination with tacrolimus and corticosteroids
- In patients with severe renal impairment, avoid > 2 g/day doses
- If neutropenia develops, reduce the dose or stop mycophenolate mofetil
- Fruit-flavoured MMF suspension available
  - 1 gram/5mL, 2 month shelf life
- MMF injection available if necessary
  - Same dose iv as oral
  - Requires aseptic manipulation
- Enteric coated mycophenolic acid (Myfortic):
  - Adults: 720 mg po BID

Safety Profile

Mycophenolate

- No hepatotoxicity, neurotoxicity, or nephrotoxicity
- Primary adverse effects include:
  - Nausea, diarrhea, vomiting
  - Neutropenia, thrombocytopenia, anemia
  - < 1% Progressive multifocal leukoencephalopathy
**Therapeutic Drug Monitoring**

**Mycophenolate mofetil**
- No routine therapeutic drug monitoring at this time
  - monitor ADRs, and impact of drug interactions
- Avoid use with azathioprine - increase toxicities
- If ANC <1500 interrupt dosing or ↓ dose
- Avoid doses >1000mg BID with GFR < 25mL/min

**Conclusions**

**Mycophenolate**
- Use in OLT recipients suggests reduced rejection rates and improved survival when added to tacrolimus and steroids
- Many Generic Formulations are available
  - Enteric coated mycophenolic acid (Myfortic) available as well
- Use in OLT recipients:
  - tacrolimus sparing (to reduce kidney and nervous system side effects)
  - steroid sparing

**Sirolimus (Rapamune®)**
- Used for preventing rejection after OLT
  - Usually not started sooner than 4 weeks after transplant
  - Used in OLT recipients that have side effects from tacrolimus
  - Used in OLT recipients that have graft dysfunction
### Adverse Effects

**Sirolimus**

- Hyperlipidemia
  - Increased risk when used with CSA and steroids
  - Usually requires diet and "statin" therapy
    - Get baseline lipid profile, then follow up in 2 weeks after starting sirolimus therapy
- Thrombocytopenia
- Nausea, diarrhea, increased LFTs
- Acne and rash
- Slows wound healing
- ? HAT
- Minimal nephrotoxicity, neurotoxicity, diabetes

### Dose and Monitoring

**Sirolimus**

- Dose (liver tx): Loading dose: 3 mg PO on first day followed by 1-2 mg PO QD
- Monitoring levels:
  - 5-10 ug/ml when given with tacrolimus
  - No need to monitor daily levels of sirolimus

### Summary

**Sirolimus**

- **Benefits**
  - Less nephrotoxicity/neurotoxicity than tacrolimus or cyclosporine
  - May allow a reduced dose or tacrolimus free immunosuppressive regimen
- **Concerns**
  - Not adequate as a single agent (can’t be used alone)
  - Risk of early HAT?
  - Poor wound healing
  - Causes lipid problems
  - Interactions with many medications
**Everolimus (Zortress)**
- In April 2010, the FDA approved everolimus for prevention of organ rejection; similar to sirolimus
- Dose: 0.75 mg orally twice daily (1.5 mg/day) for adult transplant patients
- Target Trough levels: 3–8 ng/mL, (side effects more likely to occur with levels >12 ng/mL)
- Adverse effects
  - Peripheral edema, constipation, hyperlipidemia, hypertension, nausea, thrombocytopenia, anemia

**Other Immunosuppressive Agents**
- Basiliximab (Simulect):
  - Use:
    - May decrease the incidence of acute rejection
    - Allows for reduced dose or delayed start of maintenance agents such as tacrolimus in the early postoperative period to help reduce side effect such as kidney dysfunction
    - Dose: 20 mg IV on day 0 and post operative day 4
      - Very few side effects
      - expensive

- Thymoglobulin (rabbit):
  - Use:
    - Treatment of steroid resistant rejection
    - Many side effects
      - Fevers, chills, hypotension
      - Infection (CMV, fungal, Pneumocystis)
      - Blood dyscrasias
    - Follow thymoglobulin protocol
Individualizing Immunosuppression

- Selection of immunosuppression is based on:
  - Efficacy (how the drugs work)
  - Short-term and long-term outcome information
    - Patient and allograft survival
    - Biopsy-proven rejection rates
  - Toxicity
  - Short-term, long-term adverse effects
  - Other:
    - Clinical training, anecdotal experience
    - Recognized risk factors in a transplant population
    - Cost

Infectious Complications in Liver Transplantation
Infection in Liver Transplant

**Background**
- Infection can be a life threatening complication following transplantation
- Transplant recipients are unique hosts because
  - impaired state of health pre-transplant
  - undergo technically complex procedure
  - post-operative immunosuppression
- Broad range of potential pathogens
- Early diagnosis/treatment of infections are essential to reduce morbidity/mortality

**Risk Factors**

**Epidemiologic Exposure**
- Community
  - viruses
  - *Listeria monocytogenes*
  - *Campylobacter jejuni*
  - *Strongyloides stercoralis*
  - endemic mycosis
- Hospital: domiciliary/non-domiciliary
  - Gram negative rods and *Pseudomonas* spp.
  - *Legionella*
  - *Aspergillus*
  - VRE, MRSA, *Clostridium difficile*

**Risk Factors for Infection**

<table>
<thead>
<tr>
<th>Pre-transplant Medical Condition</th>
<th>Transplant Surgery</th>
<th>Post-transplant Hospital Flora</th>
<th>Post-op management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hepatitis</td>
<td>Prolonged procedure</td>
<td>Resistant bacteria</td>
<td>Catheter</td>
</tr>
<tr>
<td>Heart disease</td>
<td>Multiple transfusions</td>
<td>Aspergillus/ <em>Legionella</em></td>
<td>TPN, neutropenia</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Graft ischemia</td>
<td></td>
<td>Prolonged intubation</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>Graft injury</td>
<td></td>
<td>Prolonged antibiotics</td>
</tr>
<tr>
<td>Latent infections</td>
<td>Bowel leak</td>
<td></td>
<td>Repeat laparotomy</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
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<tr>
<td>Herpes simplex virus</td>
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<tr>
<td>Varicella zoster virus</td>
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<tr>
<td>Tuberculosis</td>
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<tr>
<td>Colonization</td>
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<tr>
<td>Preop antibiotics</td>
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<td></td>
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<tr>
<td>Preop hospitalization</td>
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<tr>
<td>Immunosuppression</td>
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<tr>
<td>Ciclosporine, MMF (?)</td>
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<tr>
<td>Tacrolimus, sirolimus</td>
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<td></td>
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<tr>
<td>Corticosteroids, ATG</td>
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</tr>
</tbody>
</table>

*Emmanouelides et al.*
**Timecourse for Infection**

- **VIRAL**
  - HSV
  - CMV ONSET
  - EBV, VZV, RP, ADENOVIRUS
  - CMV CHORIORETINITIS

- **FUNGAL, TB, PNEUMOCYSTIS**
  - CNS
  - LISTERIA
  - ASPERGILLUS, Nocardia, TROMPLERIA
  - CRYPTOCOCCUS

- **BACTERIAL**
  - WOUND
  - LINE-RELATED, INTRA-ABDOMINAL
  - BILIARY TRACT BACTEREMIA
  - UTI

- **INTRA-ABDOMINAL**
  - CMV

- **WOUND-RELATED**
  - CMV CHORIORETINITIS

- **UTI**

**Infection in Liver Transplant**

**Management Strategies**

- **Prophylaxis:** antimicrobial used to prevent a common infection
  - Example: TMP/SMX for PCP in transplant recipients; amp/sulb for surgical prophylaxis

- **Empiric:** institution of antimicrobial treatment based upon all clinical information without knowledge of a pathogen
  - Example: piperacillin/tazobactam for FUO

- **Therapeutic/directed:** antimicrobial used to treat an established (documented) infection
  - Example: ceftazidime plus gentamicin for *Pseudomonas aeruginosa* bacteremia

- **Pre-emptive:** antimicrobial used in a subgroup of patients prior to appearance of clinical disease at the time of “high risk” of infection
  - Example: ganciclovir given following thymoglobulin for high risk of CMV disease
Routine Antibiotic Prophylaxis for Procedures

**LIVER TRANSPLANTATION**

<table>
<thead>
<tr>
<th>All patients</th>
<th>Oral neomycin 1.0 gram po q1hr x 4 doses plus oral erythromycin base 1.0 gram po q1hr x 4 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-penicillin allergic</td>
<td>ampi/sulb 3.0g IVPB OCl then q 6h x 24h ceftriax 1g IVPB OCl then q 24h + vanco 15mg/kg IVPB OCl then q 12h x 24h</td>
</tr>
<tr>
<td>Penicillin allergic (rash)</td>
<td>ceftriax 1g IVPB + vancomycin 15mg/kg pre/post procedure (2 doses)</td>
</tr>
<tr>
<td>Penicillin allergic (anaphylaxis)</td>
<td>gent 1.5mg/kg IVPB OCl then q 24h + vanco 15mg/kg IVPB OCl then q 12h x 24h</td>
</tr>
</tbody>
</table>

**CHOLANGIOGRAM, BILE DUCT DRAINAGE TUBE PLACEMENT/REMOVAL**

| Non-penicillin allergic | ampicillin/sulbactam (Unasyn) 3.0g IVPB pre/post procedure (2 doses) |
| Penicillin allergic (rash) | ceftriax 1g IVPB + vancomycin 15mg/kg pre/post procedure (2 doses) |
| Penicillin allergic (anaphylaxis) | gentamicin 1.5mg/kg IVPB + vancomycin 15mg/kg pre/post procedure (2 doses) |

### Bacterial Infections: POD 0-3

- **Common Infectious Syndromes:**
  - Pneumonia ± Bacteremia
  - Primary Bacteremia
  - Intra-Abdominal Infections
  - Superficial or Deep Wound Infections
  - Urinary Tract Infections
  - Vascular Catheter Infections
  - Catheter Site Infections
  - Superinfections of fluid collections or devitalized tissues

### Infection in Liver Transplant

**Bacterial Infections**

- **Initiation of therapy**
  - Initiate therapy immediately, limit duration of therapy
  - Reduces risk of resistance or fungal superinfection
  - Use broad spectrum agent empirically
  - Pip/tazo plus vanco
  - Once organism has been isolated, specific therapy “narrow spectrum” should be used
  - Assess renal function and allergy information
Management of Viral Infections in Liver Transplantation

Overview

Viral Infections in Liver Transplantation

- Spectrum of Viral Pathogens
  - CMV, EBV, HBV, HCV
- Presentation
  - direct and indirect effects
- Management Strategies
  - prophylaxis and treatment

Risk Factors Predisposing to CMV Disease in Liver Transplantation

- Absent or reduced CMV immunity:
  - CMV D+/R- or CMV+ blood transfusion to D-/R-
  - cumulative dose of potent pan-immunosuppressive agents (steroid boluses, antilymphocyte antibody thymoglobulin, mycophenolate mofetil)
- Increased reactivation of latent CMV:
  - cytokine release (TNF, IL1) by ALA and bacterial infection, stress (catecholamine)
  - virus–virus interactions
- D+/R- and ALA use accounts for 80% of CMV disease
**History**

*Why Prevent CMV in Liver Transplantation?*

- In the pre-antiviral era, CMV was a major cause of mortality, and graft loss secondary to immunosuppression.
- In solid liver transplantation CMV may cause:
  - Direct morbidity (CMV disease) ranging from viral syndromes to demonstrated organ involvement.
  - Indirect associated complications:
    - acute and chronic graft rejection
    - decreased patient survival
    - opportunistic infections: fungi and EBV
    - increased cost to transplant program
    - accelerated atherosclerosis

**Direct Effects**

*Cytomegalovirus in OLT*

- Flu-like syndrome: fever, malaise, arthralgias, nausea, vomiting
- Hematologic changes:
  - Leukopenia
  - Atypical lymphocytosis
  - Thrombocytopenia
- Gastrointestinal: ulceration, diarrhea
- Specific organ involvement:
  - Liver: hepatitis
  - Lungs: pneumonitis
  - GI tract: enteritis

**Treatment/Prevention of CMV**

- **Treatment CMV Disease:** ganciclovir 5mg/kg q 12h IV x 14-21 d; change to oral valganciclovir (900mg po bid) once patient improves to complete therapy.
  - Adjust dose for AE, renal function
  - Monitor clinical manifestations, CMV PCR
- **CMV Prophylaxis:** ganciclovir 5mg/kg IV qd from day 1 after OLT to day of DC; after DC, continue with valganciclovir 900mg po qd until POD # 100
  - Preemptive therapy useful in selected OLT recipients with asymptomatic CMV viremia (detected by blood PCR); start IV ganciclovir 5mg/kg q12hrs; can change to oral valganclovir (900 mg po bid) once CMV viremia decreases and continue until blood CMV PCR becomes negative.
  - If subsequently used Thymoglobulin (steroid resistant rejection), resume ganciclovir prophylaxis 6mg/kg IV QD or valganciclovir 900 mg PO QD for 12 weeks

Winston et al., Lancet 1995
Fungal Infections in OLT Recipients

Incidence of Fungal Infection in SOT

<table>
<thead>
<tr>
<th>Organ Transplant</th>
<th>Incidence of IFI (%)</th>
<th>Proportion of IFI %</th>
<th>Mortality %</th>
<th>Mortality %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Aspergillus</td>
<td>Candida</td>
<td>Aspergillus</td>
</tr>
<tr>
<td>Renal</td>
<td>0-20</td>
<td>0-26</td>
<td>78-95</td>
<td>20-100</td>
</tr>
<tr>
<td>Heart</td>
<td>5-21</td>
<td>77-91</td>
<td>8-26</td>
<td>78</td>
</tr>
<tr>
<td>Liver</td>
<td>4-42</td>
<td>1-34</td>
<td>35-91</td>
<td>50-100</td>
</tr>
<tr>
<td>Lung/heart-lung</td>
<td>10-36</td>
<td>20-60</td>
<td>42-73</td>
<td>21-100</td>
</tr>
<tr>
<td>Small bowel</td>
<td>33-59</td>
<td>0-4</td>
<td>80-100</td>
<td>0-100</td>
</tr>
<tr>
<td>Pancreas, P/K</td>
<td>6-38</td>
<td>0-3</td>
<td>97-100</td>
<td>100</td>
</tr>
</tbody>
</table>

Sites of Infection

Candidiasis

- **Severity:** local invasive, disseminated, or uncomplicated w/o evidence of tissue invasion
- **Onset/symptoms:** sudden fever, chills, malaise, insidious presentation
- **Candidal syndromes:**
  - catheter related sepsis
  - cellulitis
  - intra-abdominal abscess
  - pulmonary infection
  - urinary tract (cystitis)
  - arthritis, esophagitis
  - endocarditis, mediastinitis
  - menigitis
  - ophthalmitis
  - hepatosplenic
Sites of Infection
Aspergillosis

- **Severity**
  - localized or disseminated disease
  - once disseminated, often fatal complication

- **Onset/Symptoms**
  - within first 2-3 months post-transplant
  - pulmonary symptoms (nonproductive cough, chest pain, SOB)
  - low grade fever, MS changes, seizures, IA, etc

- **Clinical Syndromes**
  - Pulmonary
  - Cutaneous
  - Sino-orbital
  - Heart
  - GI tract
  - Bone and joint
  - CNS
  - Liver, spleen, kidneys

Antifungal Agents

- **Systemic antifungals**
  - **Triazoles**
    - Fluconazole (Diflucan®)
      - UCLA prophylaxis protocol: 400 mg PO QD x 42 days (regular risk); adjust for renal dysfunction
    - Voriconazole (Vfend®)
      - Used for prophylaxis in high risk OLT patients only
      - If patient at high-risk for aspergillosis (on steroids pre OLT, aspergillus colonization of respiratory tract), voriconazole 200-300 mg po q12hrs x 42 days
      - DOC for invasive aspergillosis
  - **Echinocandins**
    - Caspofungin acetate (Cancidas®)
      - Used to treat candida infections; not routinely used for prophylaxis
  - **Polyenes**
    - Amphotericin B (Fungizone®, Abelcet, AmBisome)
    - Rarely used due to nephrotoxicity

Infection in Liver Transplant
Pneumocystis Infection

- **Clinical manifestations**
  - fever, dyspnea
  - non-productive cough
  - interstitial infiltrates
  - hypoxemia
  - asymptomatic

- **Diagnosis**
  - BAL, lung biopsy
  - methenamine silver stain
  - monoclonal antibodies
Pneumocystis Management Strategies

- **Treatment:**
  - TMP/SMX 20mg/kg/d in 3-4 divided doses IV

- **Prophylaxis:**
  - TMP/SMX 1 DS tab po qd x 1 yr (preferred)
  - TMP/SMX 1 DS tab po tid (Sat, Sun only)
  - TMP/SMX 1 DS tab po bid (Mon, Wed, Fri)

- **Bactrim allergy**
  - Atovaquone (preferred)
  - dapsone
  - pentamidine (rarely used)

Infection in Liver Transplant

**Summary**

- Infections are common in transplant recipients
- Multiple host factors place transplant recipients at risk for infection
- Identification of these factors/patients may minimize morbidity/mortality
- Rapid diagnosis and treatment are essential for eradication/suppressing infection

Questions?