Heart Transplantation Immunosuppression, Rejection & Opportunistic Infection Treatment

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No disclosures
Overview

• History of immunosuppression
• Induction agents
• Overview of Immunosuppressants
• Overview of prophylactic preventative medications
• Treatment for rejection
History of Immunosuppression

- **1954**: First successful renal transplant
  - Identical twin donor w/o immunosuppression
- **1959**: First successful allograft
  - Non-identical twin
  - Sublethal total body irradiation
- **1960s**: First successful unrelated allograft
  - Azathioeprine
  - >1 yr survival
- **1963**: Reversal of rejection with steroids
- **1967**: First Heart Transplant—died of rejection in several days
Immunosuppression Theory

• When choosing immunosuppressive therapy do we...?
  a. Maximally utilize one agent
  b. Avoid toxic medications
  c. Utilize a multidrug regimens
Immunosuppression Theory

Multi-drug therapy--Why?

– Any 1 agent, if used at high doses, could prevent rejection
– Multidrug regimens allow for lower doses of each, minimizing toxicity, while providing adequate immunosuppression
– Works at different pathways on immune response cascade
Goals when choosing immunosuppression

• Minimize adverse effects
• Provide adequate immunosuppression
• Screen for drug related complications and treat effectively
Induction Therapy
Induction Therapy

• Provides intense activity
• Long Acting Effects
• Provides immunosuppression during critical pre-operative stage
• Provides immunosuppression post op during complications
Induction Therapy

- ATGAM (Equine)
- Thymoglobulin (Rabbit)
- Basiliximab
- Alemtuzumab
- OKT3
Antibody Preparations

-Thymoglobulin

- Polyclonal antithymocyte globulin
- Immunizing rabbits with human lymphoid cells derived from thymus or cultured B cell lines.
- Induction and rejection
Thymoglobulin

- Dose is 1.5mg/kg IV daily
- First infusion is over 6 hours, subsequent over 4 hours
- Central line through 0.22 micron filter
- Premedicate with methylprednisolone, diphenhydramine, acetaminophen
- Side effects: allergic and immune reactions, increased risk for infection, CMV
Antibody Preparations

• Campath
  – Humanized Monoclonal antibody
  – anti CD-52

• Induction/rejection

• Side effects: first dose reactions, neutopenia, anemia, infections
Campath Induction Protocol

- 30mg POD 0 some protocols give 2\textsuperscript{nd} dose POD 4
- Adjust dose for patient <40kg
- Infuse over 3 hrs
- Premedicate: methylprednisolone, acetaminophen, diphenhydramine, famotidine, ondansteron
IL-2 Antagonist

• Basiliximab
  – Binds to T-lymphocyte IL-2 receptor alpha chains (antagonizing IL-2)
  – 20mg IV x 2 doses, POD 0 and POD 4
  – Side effects: leukopenia, anaphylaxis/hypersensitivity.
Analysis is limited to patients who were alive at the time of the discharge.
Calcineurin Inhibitors

• Block interleukin 2 (IL-2) production ultimately preventing activation of T-cells and the immune cascade in general
Calcineurin is responsible for transcription of cytokines leading to T cell activation. This is a 3 signal pathway of T cell activation, now inhibited by CNI.
Calcineurin Inhibitors

Cyclosporine (Sandimmune/Gengraf/Neoral)

- Multiple formulations
  - Oil based (variable absorption)
  - Microemulsion (preferred)
  - Products are not interchangeable
Cyclosporine Dosing

- PO: q 12 hrs at 4-8 mg/kg/day
- IV: q 12 hr infusions or continuous IV infusion
- IV is 1/3 daily oral dose
- Troughs 250-350ng/mL
- Available 25mg, 100mg
Cyclosporine Adverse Events

- Renal insufficiency
- HTN
- Dyslipidemia
- Hypokalemia
- Hypomagnesemia
- Hyperuricemia
- Neurotoxicity (encephalopathy, seizures, tremors, neuropathy)
- Gingival hyperplasia
- Hirsutism
Calcineurin Inhibitors

Tacrolimus

• FK-506
• Most commonly used CNI
• Side effects:
  – HTN, DM, hyperkalemia, nephrotoxicity, neurotoxicity, PTLD
Tacrolimus dosing

- **PO:** q 12 hrs at 0.05-0.1 mg/kg/day
- **IV:** continuous infusion, difficulties
- **Trough 10-15ng/mL**
- **Available 0.5mg, 1mg and 5mg**

- Oral Dose = 3-4 times the IV dose
- Sublingual Dose = ½ the PO dose
- IV- 1/3 of daily oral dose
Sublingual Tacrolimus dosing in Transplant

• Who qualifies?
  – Transplant patients who are intubated/GI complication/NPO

• Advantages
  – Sublingual administration improves absorption via non-GI pathway (twice the absorption of oral)
  – Useful in post transplant cystic fibrosis patients & patients with poor gastric emptying
# Tacrolimus Drug Interactions

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Mechanism and Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital, Phenytoin, Rifampin, Carbamazepine</td>
<td>P450 induction → increased tacrolimus metabolism</td>
</tr>
<tr>
<td></td>
<td>Decreased tacrolimus levels</td>
</tr>
<tr>
<td>Diltiazem, Nicardipine, Erythromycin, Clarithromycin, Cimetidine, Metoclopramide, Voriconazole, Itraconazole, fluconazole</td>
<td>P450 inhibition → decreased tacrolimus metabolism</td>
</tr>
<tr>
<td></td>
<td>Increased tacrolimus levels</td>
</tr>
<tr>
<td>Grapefruit Juice</td>
<td>Inhibits tacrolimus metabolism increasing bioavailability and increasing levels</td>
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</tbody>
</table>
Drugs That May Cause Renal Dysfunction When Administered with Cyclosporine or Tacrolimus

- Amphotericin
- Cimetidine
- Ranitidine
- NSAIDS
- Ganciclovir

- Vancomycin
- Tobramycin
- Gentamycin
- Tacrolimus or Cyclosporine
Antimetabolites
Antimetabolites Interfere with synthesis of nucleic acids and exert effects by inhibiting B and T cell proliferation.
Anti-Metabolites

Cellcept/mycophenolate mofetil (MMF)
   – Inhibitor of DNA/RNA synthesis, thereby suppressing lymphocyte proliferation and antibody production

Myfortic/mycophenolic acid
   – same mechanism of action as MMF, but enteric coated
     • Side effects:
       – Leukopenia, anemia, GI
Mycophenolate Mofetil

- PO: 500mg tablet and 250mg capsule, dosed 500-1500mg BID
- IV: same dose as PO, 2 hours infusion every 12 hours
- Levels not monitored
- Side effects
  - GI (nausea/vomiting/diarrhea)
  - Leukopenia and thrombocytopenia
  - Pancreatitis, hypercholesterolemia, elevated LFT’s
Mycophenolate Mofetil

- Category X
- REMS program
Imuran (Azathioprine)

- Prodrug hydrolyzed for 6-Mercaptopurine
- Inhibits enzyme for DNA synthesis
- Older agent
- Used when intolerance to Cellcept or Myfortic
Imuran (Azathioprine)

- IV same as PO dose
- Levels not monitored
- 50 -150mg PO QD
- Monitor : CBC and LFTs
- Side effects:
  - Leukopenia, thrombocytopenia, anemia
  - Pancreatitis
  - Hepatitis
Proliferation Signal Inhibitors
(MTOR Inhibitors)
Inhibit a protein kinase called mammalian target of rapamycin (mTOR) that is involved in transduction signals from the IL-2 receptor to the nucleus causing cell cycle arrest (inhibits both B and T cell proliferation in response to cytokine signals)
Sirolimus

Dosing:
• PO: available as liquid or tablet
• 1-3 mg daily
• Trough 5-10 ng/mL
• Interacts with cyclosporine; must be dosed ≥4 hrs apart

Adverse Events:
• Oral ulcers
• Dyslipidemia
• Poor wound healing
• Edema
• Pneumonitis, alveolar hemorrhage
• Bone marrow suppression (anemia and thrombocytopenia)
Everolimus (Zostress)

- Analog of sirolimus
- Approved for renal transplantation
- Starting dose 0.75mg every 12 hours
Corticosteroids
Nonspecific immunosuppressant that interrupts multiple steps in immune activation, including antigen presentation, cytokine production, lymphocyte proliferation, gene transcription, impaired APC and inflammatory cell function. Used in induction, maintenance and rejection.
Steroids

Dosing:
- 1 mg/kg/day divided into bid dosing early with rapid tapering
- PO: prednisone
- IV: methylprednisone

Adverse Events:
- Weight gain
- HTN
- Osteopenia
- Hyperglycemia
- poor wound healing
- Edema
- Gastric Ulcers
- Fluid retention
Clinical Use of Immunosuppression
Immunosuppressive Cocktail

• Calcineurin Inhibitor
  – Cyclosporine
  – Tacrolimus
• Anti-metabolite
  – Azathioprine
  – Mycophenolate mofetil
• Steroids
Analysis is limited to patients who were alive at the time of the follow-up.
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Adult Heart Transplants
Maintenance Immunosuppression at Time of 1 Year Follow-up by Year

**NOTE:** Different patients are analyzed in each timeframe.

Analysis is limited to patients who were alive at the time of the follow-up.
Managing Side Effects

Tacrolimus

Tremor
  • Level Toxic
  • Adjust dose
  • Clonazepam

Nephrotoxicity
  • Adjust dose
  • Consider alternative agent

Hyperlipidemia
  • Treat appropriately
Managing Side Effects

• Mycophenolate
  Anemia
  Neutropenia
    • Adjust dose
GI effects
  • Adjust dose
  • Consider changing to AZA
**Belatacept (Nulojix)**

Selective costimulation blocker by binding CD80 and CD 86 receptors on APC.

Dosing: 10mg/kg Day1, and 5., followed by 10mg/kg end of week 2, 4, 8, 10. Then 5mg/kg every 4 weeks
Prophylactic Medications
Post Transplant
Prophylaxis of Cytomegalovirus (CMV)
Valcyte (valganciclovir)

- A valine ester prodrug of ganciclovir with improved oral bioavailability (50-60%)
- Inhibits viral DNA polymerase
- PO: 450mg-900mg daily dose
- Adverse effects: severe leukopenia, thrombocytopenia, anemia, renal dysfunction
Valcyte (valgancyclovir)

- D+, R- Highest Risk
- D+, R+ Intermediate Risk
- D-, R+ Intermediate Risk
- D-, R- Lowest Risk
CMV Prophylaxis

• Thymoglobulin increases risk for CMV
• Corticosteroids increase the risk for CMV
• Newer immunosuppressants increase the risk for CMV
Other Antivirals

- **Gangciclovir (Cytovene)**
  - 5mg/kg IV q12hrs

- **ValACYclovir (Valtrex)/ Acyclovir**
  - CMV -/
  - 1000mg daily
  - 400mg BID
Antivirals

• Cytomegalovirus Immune Globulin (Cytogam)
  – Used for recipients who are CMV-negative and receive an organ from a CMV-positive donor.
  – Dose: 150mg/kg every 2 weeks x 6 doses
Resistance to ganciclovir/valganciclovir

- Cidofovir or Foscarnet with or without full or ½ dose ganciclovir
- High dose ganciclovir
  - Up to 10mg/kg BID
  - Significant bone marrow suppression
- Add IVIG or CMVIG
  - Questionable benefit
Cidofovir

- Nucleoside analogue
- Viral DNA polymerase inhibitor
- Used concurrently with a reduction in immunosuppression.
- Side effects: renal impairment, neutropenia
Foscarnet

• Pyrophosphate analogue which acts as a noncompetitive inhibitor of many viral RNA and DNA polymerases as well as HIV reverse transcriptase

• Virostatic

• Side effects: renal impairment, seizures
Prophylaxis of Pneumocystis Carinii (PCP)
PCP Prophylaxis

• Sulfamethoxazole/Trimethoprim (SMZ/TMP)
  – Dose is SS (400mg/80mg) daily or DS TIW
  – Side Effects: hyponatremia/hyperkalemia, renal dysfunction

• Dapsone
  – Dose is 100mg weekly
  – Side Effects: neuropathy, methemoglobinemia, anemia, hepatotoxicity
PCP Prophylaxis

- Atovaquone (Mepron)
  - Dosing: 1500mg daily (take with OJ)
  - Side Effects: elevated LFT, anemia

- Inhaled Pentamididine
  - Dosing: 300mg every 4 weeks
Prophylaxis of Thrush
Thrush Prophylaxis

• Clotrimazole Troches
  – 10mg TID
• Nystatin suspension
  – 5mL swish and swallow QID

  – Patients cannot eat or drink For 30 minutes after use.
Antifungals

• Voriconazole (Vfend)
  – Load 6mg/kg IV q12h x 2 doses, 200mg PO BID
  – **Reduce tacrolimus by 1/3
  – **Reduce cyclosporine by ½

• Posaconazol (Noxafil) DR
  – 300mg bid x 1 day, 300mg daily
  – **Reduce tacrolimus by 1/3
  – **Reduce cyclosporine ¼
  – Use with fatty foods
Antifungals

• Cresemba
  – 372mg IV q8h x 6 doses, then 372mg daily IV or PO
  – **Reduce tacrolimus by 1/3
  – **Reduce mTOR by ¼

• Abelcet
  – 25mg inhaled via nebulizer once a week

• Amphotericin B
  – 20mg inhaled via nebulizer q12hrs
Rejection

• The type of therapy used to treat an acute rejection episode depends upon the histologic severity, the degree of hemodynamic compromise and/or symptoms, and the number of rejections immediately preceding the rejection to be treated.
<table>
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<tr>
<th>Grade</th>
<th>Histopathologic findings</th>
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<tbody>
<tr>
<td>0R, none</td>
<td>None</td>
</tr>
<tr>
<td>1R, mild</td>
<td>Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage</td>
</tr>
<tr>
<td>2R, moderate</td>
<td>Two or more foci of infiltrate with associated myocyte damage</td>
</tr>
<tr>
<td>3R, severe</td>
<td>Diffuse infiltrate with multifocal myocyte damage ± edema ± hemorrhage ± vasculitis</td>
</tr>
</tbody>
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*From Stewart et al JHLT, 2005*
ACR Treatment

- Corticosteroids
  - Major action to inhibit the synthesis of cytokines.
  - High-dose, pulse
  - Suppress production of IL-1, diminishing production of IL-2 and weakening the cellular immune response
ACR Treatment

• Antithymocyte globulins
  – Thymoglobulin or ATGAM
    • Reverse rejection by cell death by compliment-dependent lysis.
    • No comparative data of using either
    • CD3 monitoring helps adjust dose and frequency
ACR Treatment

• OKT3
  – Monoclonal antibody
  – Causes shredding of CD3 T-cell complex
  – Significant side effects so not used in most clinical rejection episodes.
    • Cytokine-mediated reactions (fever, rigors, chills, hypotension, chest pain, wheezing)
    • Infection
    • Pulmonary edema
AMR

• Optimal therapy not well defined
• Treat if AMR severe enough to cause hemodynamic compromise?
• Plasmapheresis, steroids, antilymphocyte antibodies, rituximab.
Summary

• Numerous options and immunosuppression has improved greatly since the beginning
• Three drug cocktail is standard of care using a dosing taper with steroids
• Provide adequate immunosuppression while minimizing adverse events.
• Despite protocols...always treat the patient
• Patient Challenges (side effects, compliance)