Post-Transplant Immunosuppression

Christie Truscott, PharmD
Program Director, Clinical Transplant Pharmacy
Liver Transplant, Clinical Pharmacist

Jennifer Gray, PharmD
Thoracic Transplant, Clinical Pharmacist
Vanderbilt University Medical Center
Objectives

- Describe the concepts of immunosuppression and allograft rejection in solid organ transplantation
- Identify immunosuppression drugs used in transplant patients and their specific targets in the immune system
- Identify important considerations of immunosuppressive therapy in specific organ transplant patients
- Analyze potential beneficial and adverse effects of select immunosuppression medications
PATIENT CASE
Patient Case

- Mr. HK is a 52 yo Caucasian m diagnosed with alcoholic cirrhosis in 2009. He was transferred to VUMC on 6/13/2012 with encephalopathy, worsening LE edema and renal failure. His hospitalization was complicated by LLL aspiration pneumonia, *pseudomonas* pneumonia, and *candida albicans* bacteremia. He was treated with appropriate antibiotics and antifungals.
Patient Case

• Mr. HK underwent LT on 9/1/2012. His blood loss was 12L. He received 17U PRBC, 30U FFP, and 3 Plts. He was extubated 24 hours post-op. His transplant medication regimen was initiated intraoperatively with 500 mg IV methylprednisolone and prophylactic antibiotics per protocol.
Pharmacotherapy of Solid Organ Transplantation

- Induction Immunosuppression
- Maintenance Immunosuppression
- Allograft rejection
Induction Immunosuppression

• Short-term, intense perioperative immunosuppression

• Powerful immunosuppression decreases incidence of early acute allograft rejection
  – Toxicities and infectious risk preclude long-term use

• May be in the form of high-dose corticosteroids or antibody preparations
Maintenance Immunosuppression

• Long-term immunosuppression that is lower in potency and infectious risk
  – Side effects contribute to considerable morbidity and mortality
• Decreases incidence of chronic allograft rejection and damage
• Most commonly in the form of oral medications
  – Calcineurin inhibitors (tacrolimus, cyclosporine)
  – Mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus)
  – Antimetabolites (mycophenolate mofetil, azathioprine)
  – Low-dose corticosteroids
### Allograft Rejection

- **Hyperacute**
  - Minutes to hours
  - Very uncommon

- **Acute**
  - Days to weeks
  - Cellular-mediated and/or antibody-mediated

- **Chronic**
  - Months to years
  - Antibody and cellular components

**Antibody-mediated (“humoral”) rejection:**
- Induced by B lymphocytes/antibodies

**Cellular rejection:**
- Induced by T lymphocytes

Adapted from: Chan L. *Diseases of the Kidney*. Schrier RW and Gottschalk CW (Ed.): 1997
Immunosuppression

Transplant

Maintenance

Rejection
Brief History of Immunosuppression

Pre-1980s:
- Irradiation
- Corticosteroids
- azathioprine

1983:
cyclosporine

1985

1990

1995

2000

2001:
alemtuzumab

2005

2010

1993:
tacrolimus

1997-1999:
basiliximab
rituximab
anti-thymocyte
globulin

Why do we need immunosuppression?

Prevention of Rejection

Pharmacotherapy of Solid Organ Transplantation

- Induction Immunosuppression
- Maintenance Immunosuppression
- Allograft rejection
Depleting vs. Non-Depleting

- **Depleting Agents**
  - Results in cell lysis
  - Destroys cell and prevents proliferation

- **Non-Depleting Agents**
  - Block receptor to prevent proliferation
Monoclonal Antibodies

- Non-Depleting Agent
  - Basiliximab (Simulect®)
    - Use
      - Induction
      - NOT used for rejection treatment

- Depleting Agent
  - Alemtuzumab
    - Use
      - Induction
      - Treatment of steroid resistant rejection
basiliximab (Simulect®)

- Chimeric murine monoclonal antibody directed against the interleukin-2 receptor complex (IL-2R), also known as CD25
- Inhibits T cell activation and proliferation
- **Non-depleting:** does not lyse T cells

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basiliximab (Simulect®)

• **FDA-Approved Indication**
  - Prophylaxis of acute organ rejection in patients undergoing renal transplantation

• **Transplant application at VUMC**
  - Induction immunosuppression in lung transplant
  - Induction immunosuppression in select kidney transplant recipients (e.g. HIV+, previous transplant)
basiliximab (Simulect®)

- **Contraindication:** hypersensitivity to mouse proteins

- **Cautions**
  - Increased risk of infection
  - Increased malignancy risk
  - Potential for hypersensitivity reaction

- **Adverse reactions**
  - Hypertension
  - Peripheral edema
  - Headache
  - Fever
  - Nausea, vomiting, diarrhea

Basiliximab is generally well-tolerated
basiliximab (Simulect®)

• Dosing:
  basiliximab 20mg IV x 2 doses  
  (POD 0 and POD 3 or POD 4)

• May be administered centrally or peripherally as bolus injection or infusion over 20-30 minutes
  – No premeds needed
  – Higher rates of nausea, vomiting, and injection site reactions with bolus administration

• Pharmacokinetics
  – Half-life: ~7 days
  – Duration of (incomplete) IL-2R saturation: 2-6 weeks
basiliximab (Simulect®)

Induction immunosuppression in lung transplantation

• Clinical studies: small patient numbers, inconsistent results

• Used for induction immunosuppression generally regarded as preferable to no induction

• Most centers use some form of antibody-based immunosuppression; basiliximab is largely the antibody of choice
basiliximab (Simulect®)

- Retrospective cohort study of adult lung transplant recipients (n=3970) conducted in 2008
  - No induction (n = 2249)
  - IL-2R antagonist (n = 1124)
  - Antithymocyte globulin (n= 597)

- Graft survival at 4 years significantly improved in patients receiving IL-2R antagonists versus ATG and no induction (64% vs. 60% vs. 57%; p = 0.0067)
alemtuzumab (Campath®)

- Humanized murine monoclonal antibody against CD52
  - CD52 is a cell surface glycoprotein found on B and T lymphocytes, NK cells, monocytes, and macrophages

- Mechanism of Action
  - Induces antibody-dependent lysis of CD52-positive cell types

alemtuzumab (Campath®)

• FDA-Approved Indication
  – B-cell chronic lymphocytic leukemia (B-CLL)
  – Currently under investigation for the treatment of multiple sclerosis

• Transplant application at VUMC
  – Induction immunosuppression in kidney transplantation
  – Rejection (lung)
alemtuzumab (Campath®)

Cautions/Adverse Effects

• Infusion-related reactions
  – Rigors
  – Fever
  – Nausea/vomiting
  – Hypotension
  – Shortness of breath
  – Chills
• Anemia, neutropenia, thrombocytopenia
• Increased risk of infection
• Increased malignancy risk
alemtuzumab (Campath®)

• Dosing:
  alemtuzumab 30 mg IV x 1 dose (perioperatively)

• Premedications
  – Methylprednisolone 125mg IV x 1
  – Diphenhydramine 50mg IV x 1
  – Acetaminophen 650mg PO x 1
  – Famotidine 20mg PO x 1

• May be diluted in 0.9% Sodium Chloride USP or 5% Dextrose in Water USP
  – Use within 8 hours of dilution
  – Administer via 5 µm filter
  – May also be administered subcutaneously

• Pharmacokinetics
  – Half-life: 12 hours – 6 days
  – Myelosuppression lasts for months to years
alemtuzumab (Campath®)

Alemtuzumab Induction Therapy in Kidney Transplantation: A Systematic Review and Meta-Analysis

Robert D. Morgan,1,2,3 John M. O’Callaghan,1,2,3 Simon R. Knight,1,2,3 and Peter J. Morris1,2,3,4

- Meta-analysis of 10 randomized controlled trials (n = 1223) – May 2012
- Alemtuzumab vs. IL-2R antagonists, rATG, or no antibody therapy for induction immunosuppression in kidney transplantation

- **Primary Outcome**
  - Incidence of Biopsy-proven acute rejection (BPAR)

- **Secondary Outcomes**
  - Graft loss, delayed graft function
  - Renal function
  - Patient death
  - Infection
  - Malignancy
alemtuzumab (Campath®)

- **Results**

<table>
<thead>
<tr>
<th>Induction agent</th>
<th>Outcome</th>
<th>Studies, n</th>
<th>Patients, n</th>
<th>Meta-Analysis</th>
<th>Relative risk</th>
<th>95% CI</th>
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<td>Fixed</td>
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<td>659</td>
<td>Fixed</td>
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<td>Fixed</td>
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<td>0.16</td>
<td>0</td>
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</table>

* Relative risk less than 1 favors alemtuzumab.

* P value for Cochran Q test for heterogeneity.

BPAR, biopsy-proven acute rejection (Banff grade ≥2); CI, confidence interval; DGF, delayed graft function; IL-2RA, interleukin-2 receptor antibody; NODAT, new-onset diabetes mellitus after transplantation; rATG, rabbit antithymocyte globulin.
alemtuzumab (Campath®)

• **Infection**
  – 8 studies: no significant differences in infection rates
  – Hanaway et al. (n=474) reported lower infection rates with alemtuzumab vs. antithymocyte globulin, but higher infection rates with alemtuzumab vs. basiliximab

• **Malignancy**
  – 8 studies: no significant differences in malignancy rates (follow-up periods of 30 days – 5 years)
alemtuzumab (Campath®)

- **Conclusion**
  - Alemtuzumab significantly decreases the rate of biopsy-proven acute rejection (BPAR) when compared to basiliximab
  - Rates of BPAR are not significantly different between alemtuzumab and rabbit anti-thymocyte globulin

- **In practice**
  - Basiliximab may be utilized for patients at low immunologic risk
  - The use of alemtuzumab and rabbit anti-thymocyte globulin is center-specific; largely dependent upon logistical considerations
Polyclonal Antibodies

• Depleting Agents
  – Thymoglobulin® - rabbit
    • Induction
    • Steroid resistant rejection
  – Atgam® - horse
    • Use
      – Treatment of steroid resistant rejection
    • Variable potency
antithymocyte globulin
(rATG; Thymoglobulin®)

- Rabbit polyclonal antibody against a variety of T-cell surface markers
  - CD2, CD3, CD4, CD8, CD11, CD18, CD25, CD44, CD45, HLA-DR

- Induces antibody-mediated lysis of T cells

- **FDA-Approved Indication**
  - Treatment of acute rejection in kidney transplant

- **Transplant application at VUMC**
  - Induction immunosuppression for heart transplant
  - Treatment for steroid-refractory acute cellular rejection
antithymocyte globulin (rATG; Thymoglobulin®)

Contraindications
• Allergy or anaphylaxis to rabbit proteins

Cautions
• Anaphylaxis
• Cytokine release syndrome
• Serum sickness
• Increased risk of infection
• Increased malignancy risk
antithymocyte globulin (rATG; Thymoglobulin®)

Adverse Effects

- Hypertension
- Tachycardia
- Chills, fever, headache
- Nausea/diarrhea
- Anemia, leukopenia, thrombocytopenia
- Peripheral edema
antithymocyte globulin (rATG; Thymoglobulin®)

• Dosing:
  rATG 1or 1.5 mg/kg IV q24h x 3-5 doses (POD 0 through POD 2, 3, or 4)

• Should be administered into a high flow (central) vein
  – Infuse over at least 6 hours for the first dose
    • May run each consecutive dose over 4 hours if tolerated
• Use 0.22 micron in-line filter

• Premedications
  – Methylprednisolone 125mg IV x 1
  – Diphenhydramine 50mg IV x 1
  – Acetaminophen 650mg PO x 1
  – Famotidine 20mg PO x 1

• Pharmacokinetics
  – Half-life: 30-40 days
  – Myelosuppressive effects may last up to a year
antithymocyte globulin (rATG; Thymoglobulin®)

Basiliximab and Rabbit Anti-thymocyte Globulin for Prophylaxis of Acute Rejection After Heart Transplantation: A Non-inferiority Trial

Michel Carrier, MD, a Marie-Hélène Leblanc, MD, b Louis P. Perrault, MD, PhD, a Michel White, MD, a Daniel Doyle, MD, b Danielle Beaudoin, RN, a and Marie-Claude Guertin, PhD c

• Multicenter, open-label non-inferiority trial of 35 adult heart transplant patients conducted in 2007
  – basiliximab 20mg IV x 2 (n=17)
  – rATG 125mg IV q24h x 3 (n=18)

• Primary outcome:
  – Freedom from rejection at 6 months

• Secondary outcomes:
  – Patient survival
  – Freedom from infection
antithymocyte globulin (rATG; Thymoglobulin®)

• Freedom from rejection at 6 months:
  – Basiliximab - 65%
  – Antithymocyte globulin - 83%

• Non-inferiority of basiliximab could not be established

• Patient survival and freedom from infection were similar between the groups

Figure 1. Freedom rate from acute rejection (grade 3A and 4). The 2 treatments were not equivalent. RATG, rabbit anti-thymocyte globulin; RR, relative risk.
antithymocyte globulin (rATG; Thymoglobulin®)

• Retrospective analysis of 48 adult heart transplant recipients
  – Basiliximab 20mg IV x 2 doses (n=25)
  – rATG 1.5 mg/kg IV x 3 doses (n=23)

• Outcomes assessed
  – Episodes of acute cellular rejection (evaluated via ‘Average Biopsy Score’ [ABS])
  – Life-threatening infections
  – Renal dysfunction (calculated CrCl ≤ 55mL/min)
antithymocyte globulin (rATG; Thymoglobulin®)

- Average biopsy score (ABS) lower for patients receiving rATG at 1 and 3 months ($p = 0.023$, $p = 0.032$)
- No significant difference in episodes of infection or creatinine clearance at any time point

*Figure 1. Average biopsy scores (ABS). Data are shown as means ± standard deviations. RATG, rabbit anti-thymocyte globulin*
antithymocyte globulin (rATG; Thymoglobulin®)

• Conclusion:
  – Antithymocyte globulin and basiliximab appear to be equally well-tolerated in heart transplantation
  – Antithymocyte globulin may be associated with lower rates of acute cellular rejection
Pharmacotherapy of Solid Organ Transplantation

• Induction Immunosuppression

• Maintenance Immunosuppression

• Allograft rejection
Maintenance Therapy

• Goals
  – Continual, sustained decrease in immune function
  – Prevent graft dysfunction
  – Balance toxicities, infections, and graft function
Maintenance Therapy

- Calcineurin Inhibitors
  - Cyclosporine
  - Tacrolimus

- Anti-Metabolites
  - Mycophenolate
  - Azathioprine

- mTOR inhibitors
  - Sirolimus
  - Everolimus

- Costimulatory Blockers
  - Belatacept

- Steroids
Calcineurin Inhibitors

- Tacrolimus (Prograf®, Astagraf®, FK, FK506)
Calcineurin Inhibitors

- Cyclosporine (Gengraf®, Neoral®, Sandimmune®)
Calcineurin Inhibitors

Mechanism of action of cyclosporine or tacrolimus (FK506)

Expert Reviews in Molecular Medicine © 2000 Cambridge University Press
Dosing

• Tacrolimus (FK)
  – Always administered 12 hours apart
  – Timing is very important for obtaining correct levels
  – “Normal” range is 3-12 ng/mL

• Cyclosporine (CsA)
  – Always administered 12 hours apart
  – Timing is very important for obtaining correct levels
  – “Normal” range varies, usually 100-300 ng/mL
IV Administration

• IV formulations should only be used when patient is unable to take PO
• IV form contains cremophor which maybe associated with anaphylaxis
• Mixed/stored in glass or PVC free container
• Good for 24 hours after being mixed
• PO to IV conversion
  – CsA: 1/3 PO dose
  – FK: 1/5 PO dose
Suspension Administration

• CsA suspension is available commercially
  – 100 mg/mL

• FK suspension is prepared by pharmacy
  – 0.5 mg/mL

• Stable in plastic syringes for 24 hours
Adverse Effects

• **Common**
  - Renal toxicity
  - Neurotoxicity
  - Diabetes Mellitus
  - Hypertension
  - Hypophosphatemia
  - ↑ or ↓ potassium
  - Rash/itching
  - N/V/D

• **Less Common**
  - Edema
  - Acne
  - Alopecia
  - Increased appetite
  - Bruising
  - Increased LFTs
  - Leg cramps
Adverse Effects

Cyclosporine
• Hirsutism
• Hypertriglyceridemia
• Gingival Hyperplasia
• Hypertension

Tacrolimus
• New onset diabetes after transplant (NODAT)
• Neurotoxicity
• Alopecia
CsA Adverse Effects

- Gingival Hyperplasia
- Hirsutism
CYP450 3A4 Inhibitors

- Calcium Channel Blockers
  - Diltiazem
  - Verapamil

- "Azole" Antifungals
  - Fluconazole
  - Itraconazole
  - Ketoconazole
  - Posaconazole
  - Voriconazole

- "Mycin" Antibiotics
  - Erythromycin
  - Clarithromycin

- Antiarrhythmic Agents
  - Amiodarone

- Protease Inhibitors
  - Atazanivir
  - Darunavir
  - Fosamprenavir
  - Lopinavir
  - Ritonavir

- Food
  - Grapefruit
  - Pomegranate
CYP450 3A4 Inducers

• Anticonvulsants
  – Phenytoin
  – Phenobarbital
  – Carbamazepine
  – Oxcarbamazepine

• Antituberculosis
  – Rifampin
  – Rifabutin

• Antibiotics
  – Nafcillin

• Others
  – St. Johns Wart
Anti-Metabolites

• Mycophenolate mofetil (Cellcept®, MMF)
Anti-Metabolites

- Mycophenolic Acid (Myfortic®)
Anti-Metabolites

• Azathoprine (Imuran®)
Mycophenolate Mofetil (MMF)

Mechanism of action of mycophenolate mofetil

Expert Reviews in Molecular Medicine © 2000 Cambridge University Press
Adverse Effects

Mycophenolate
- Diarrhea
- Leukopenia
- Thrombocytopenia
- GI upset
- Edema
- Hyperglycemia

Azathioprine
- Anemia
- Leukopenia
- N/V/D
- Rash
- Arthralgia
- Myalgia
- Hepatotoxicity
Mycophenolate mofetil

- Dosed every 12 hours
  - May see q 8 hr or q 6 hr dosing
  - Goal dose is 1000mg po q 12 hr
  - Commonly used with calcineurin inhibitor
- Therapeutic drugs levels not monitored
- IV to PO conversion is 1:1
- IV formulation can still cause diarrhea
- If WBC < 3, may decrease dose or hold drug
mTOR Inhibitors

- Sirolimus (Rapamune®, Rapa, SRL)
mTOR Inhibitors

• Everolimus (Zortress®)
mTOR Inhibitors

Mechanism of action of sirolimus (rapamycin)

Expert Reviews in Molecular Medicine © 2000 Cambridge University Press
Dosing

• Sirolimus
  – Administer at the same time each day
  – Timing is very important for obtaining correct levels
  – “Normal” range is 3-12 ng/mL

• Everolimus
  – Always administered 12 hours apart
  – Timing is very important for obtaining correct levels
  – “Normal” range is 3-8 ng/mL
Administration

• Administration of Sirolimus oral solution
  – Place in glass or plastic container
  – Dilute with water or orange juice
  – Patient takes solution
  – Wash cup with water or orange juice and have patient take again
## Adverse Effects

<table>
<thead>
<tr>
<th>Sirolimus/Everolimus</th>
<th>Comments</th>
</tr>
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</table>
| • Hypertriglyceridemia  
  • Hypercholesterolemia  
  • Leukopenia  
  • Thrombocytopenia  
  • Delayed wound healing  
  • Mouth ulcers  
  • Hypertension  
  • Interstitial Pneumonitis  
  • Anemia  
  • Peripheral Edema | • Pneumonitis may resolve with discontinuation  
  • Increase in dose = increase in adverse events without increase in efficacy |

**Black Box Warning for Hepatic Artery Thrombosis**
Costimulatory Blocker

• Belatacept (Nulojix®)
Belatacept

Signal 2
Costimulation is the critical second signal

Activated T cell
• Proliferation
• Cytokine production

Signal 1
Antigen triggers T-cell receptor

No costimulation
• No cell division
• No cytokine production
• Anergy
• Apoptosis

APC

MHC

TCR
Belatacept

Administration

• 30 minute IV infusion once per month
• Requires IV filter

Adverse Effects

• Peripheral edema
• Hypertension
• Fever
• Headache
• Insomnia
Corticosteroids
Adverse Effects

- Insomnia
- Nervousness
- Increased appetite
- Indigestion
- Hyperglycemia
- Diabetes Mellitus
- Hypertension
- Mood disturbances
- Arthralgia
- Cataracts
- Glaucoma
- Headache
- Seizures
- Delirium
- Acne
- Hyperpigmentation
Summary

• Cellular rejection is the most common
• IS backbone is a CNI with MMF and prednisone
• Difficult to determine the delicate balance with calcineurin therapy
  – Low levels $\rightarrow$ Rejection
  – High levels $\rightarrow$ toxicity, infection, and malignancy
• Precautions for nurses during administration
  – Do not crush, cut, or tablets
  – Wear gloves when handling medications
Pharmacotherapy of Solid Organ Transplantation

• Induction Immunosuppression

• Maintenance Immunosuppression

• Allograft rejection
Allograft rejection

[Diagram showing the process of allograft rejection with B cells, plasma cells, effector T-helper cells, and effector T-cytotoxic cells, illustrating the role of humoral and cellular immunity in the rejection process.]
Cellular rejection

- Cellular Immunity
  - Activates macrophages that have engulfed antigen
- Effector T-helper cell
  - Stimulates effector T-cytotoxic cells that bind antigen
- Effector T-cytotoxic cell
  - Destroys infected host cells
  - Virus
    - Host cells routinely present samples of cytoplasmic proteins.
  - Those cells presenting viral proteins or other abnormal proteins that signify danger are destroyed.
Acute cellular rejection (ACR)

• Treatment options
  – **Optimization of oral maintenance immunosuppression**
    • E.g. increased goal calcineurin inhibitor trough levels, increased mycophenolate mofetil dosing
  – **Corticosteroids**
    • E.g.: methylprednisolone 250-1000mg IV q24h x 2-5 days followed by prednisone taper
  – **Anti-thymocyte globulin (Thymoglobulin®, ATGAM®)**
    • E.g. Thymoglobulin 1.5 mg/kg IV q24h x 7-14 days
    • Atgam 15mg/kg IV q24h x 7-14 days
Antithymocyte globulin (Thymoglobulin®/ATGAM®) for ACR

• Systematic review of 21 trials (n = 1387)
• Evaluated benefits/risks of antibodies for treatment of ACR
  – Primarily evaluated anti-thymocyte globulins and muromonab (OKT-3)

• Objectives
  – Evaluate efficacy of antibody preparations in preventing graft loss and resolving acute rejection episodes
  – Determine benefits and adverse events for antibody preparations
Antithymocyte globulin (Thymoglobulin®/ATGAM®) for ACR

• **Results**
  
  – Antibody therapy was superior to steroid therapy in reversing ACR episodes and preventing graft loss
    • No significant difference in death, infection within 1 year
    • Malignancy rates were not reported

  – Adverse effects were less common with anti-thymocyte globulin than with muromonab-CD3 (OKT3; no longer utilized)
Antithymocyte globulin (Thymoglobulin®/ATGAM®) for ACR

• Conclusions
  – Monoclonal and polyclonal antibodies are effective options for treatment of acute cellular rejection
  – Anti-thymocyte globulins are better-tolerated when compared to muromonab-CD3
    • It is established that rabbit anti-thymocyte globulin (Thymoglobulin®) is more effective than equine anti-thymocyte globulin (ATGAM®) at preventing and resolving rejection episodes
  – Patients being treated for ACR are at increased infectious risk – prophylactic antimicrobials are utilized to prevent infection
Antibody-mediated rejection

**Humoral Immunity**
- Extracellular antigen
- B cell
- Proliferation and differentiation of activated B cell
- Memory cell
- Plasma cell
- Antibody production
- Antibodies bind antigen

**Cellular Immunity**
- Effector T-helper cell
- Activates macrophages that have engulfed antigen
- Activated macrophage

©McGraw-Hill http://www2.bc.cc.ca.us/bio16/16_adaptive_immune.htm
Antibody-mediated rejection

• Treatment options
  – Intravenous immunoglobulin (IVIG)+ Plasmapheresis (PP)
    • E.g. PP + IVIG 2g/kg (max 140g) after PP x 5 cycles
  – Rituximab (Rituxan®)
    • E.g. 375 mg/m² IV q1-2 weeks x 1-3 doses
  – Bortezomib (Velcade®)
    • E.g. 1.3 mg/m² IV twice weekly x 4 doses
rituximab (Rituxan®)

- Chimeric murine monoclonal (anti-CD20) antibody
- Mechanism of Action
  - Activation of complement-mediated B-cell lysis
  - Induces antibody-dependent, complement-dependent, and apoptotic cytotoxicity
rituximab (Rituxan®)

• FDA-Approved indications
  – Treatment of patients with relapsed or refractory CD20-positive B-cell non-Hodgkin’s lymphoma

• Transplant application at VUMC
  – Treatment of antibody-mediated (‘humoral’) allograft rejection
rituximab (Rituxan®)

- **Cautions/Adverse Reactions**
  - Severe infusion reactions (hypotension, bronchospasm)
  - Tumor lysis syndrome
  - Hypersensitivity reactions
  - Cardiovascular risk (arrhythmia, MI, cardiogenic shock)
  - Renal toxicity
  - Severe mucocutaneous reactions
  - Leukopenia
rituximab (Rituxan®)

• Dosing: rituximab 375 mg/m² IV q 1-2 wks x 1-3 doses

• Premedications
  • Methylprednisolone 125mg IV x 1
  • Diphenhydramine 25mg PO x 1
  • Acetaminophen 650mg PO x 1

• Pharmacokinetics
  – Half-life: ~ 72 hours
  – $C_{\text{max}}$ and $t_{1/2}$ increase with subsequent doses
rituximab (Rituxan®)

- Available in 100mg and 500mg single-use vials (10 mg/mL)
  - May be diluted in 0.9% sodium chloride or 5% dextrose in water

- Must be administered as an infusion (do not give IV push/bolus)

- Store at 36 - 46°F

- Protect from light

- Do not shake/do not tube
Retrospective analysis (2009) of 54 kidney transplant patients with acute humoral rejection undergoing plasmapheresis (PP) with rituximab (n=26) or PP alone (n=28)

Outcomes evaluated

- Primary: Graft and patient survival at two years
- Secondary: SCr/calculated GFR at baseline, rejection, and resolution
rituximab (Rituxan®)

- Multivariate analysis demonstrated rituximab administration as most significant factor for difference in graft survival
  - PP + rituximab: 90% graft survival
  - PP alone: 60% graft survival

- SCr/GFR did not differ significantly in salvaged kidneys at 2 years
Objectives

• Describe the concepts of immunosuppression and allograft rejection in solid organ transplantation
• Understand the pharmacotherapy of the monoclonal and polyclonal antibodies used in transplant
• Elaborate upon the applications of antibody therapy in transplant patients
• Identify important considerations of antibody therapy in transplant patients from the perspective of pharmacists and other providers
Important Considerations
Important Considerations

• Infectious risk
  – Intensive immunosuppression increases susceptibility to bacterial, viral, fungal, and protozoal infections
  – Prophylactic antimicrobials are provided in the peri- and post-operative course and may be reinstated with treatment of rejection

<table>
<thead>
<tr>
<th>Antibacterial</th>
<th>Antiviral</th>
<th>Antifungal</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP/SMX</td>
<td>valganciclovir</td>
<td>nystatin</td>
</tr>
<tr>
<td>dapsone</td>
<td>ganciclovir</td>
<td>fluconazole</td>
</tr>
<tr>
<td>pentamidine</td>
<td>acyclovir</td>
<td>itraconazole</td>
</tr>
</tbody>
</table>
Important Considerations

• Risk of post-transplant malignancy
  – Immunosuppression increases malignancy risk
    • Post-transplant lymphoproliferative disorder (PTLD)
    • Squamous and basal cell carcinomas

• Contraindication to receipt of live vaccines
  – Varicella (Varivax® and Zostavax®)
  – Measles/mumps/rubella (MMR-II®, Trimovax®, Priorix®)
  – Rotavirus (RotaTeq®, Rotarix®)
  – Intranasal influenza (FluMist®)
## Cost of Antibody Preparations

<table>
<thead>
<tr>
<th>Product</th>
<th>AWP</th>
</tr>
</thead>
<tbody>
<tr>
<td>basiliximab (Simulect®)</td>
<td>$4509 for 2 doses</td>
</tr>
<tr>
<td>rabbit anti-thymocyte globulin (Thymoglobulin®)</td>
<td>$7,621 for 4 doses (70 kg patient)</td>
</tr>
<tr>
<td>alemtuzumab (Campath®)</td>
<td>$5,537 per 30 mg dose</td>
</tr>
<tr>
<td>rituximab (Rituxan®)</td>
<td>$10,127 for 3 doses (1.73 m²)</td>
</tr>
</tbody>
</table>
PATIENT CASE
Discharge Medications

• Tacrolimus 7 mg po BID
• Cellcept 1000 mg po BID
• Prednisone taper
• Bactrim DS 1 tablet BID on Mondays
• Valcyte 450 mg po BID
• Nystatin S & S QID

• Omeprazole 40 mg po daily
• Lantus 10 units SQ qHS
• Novolog sliding scale QID
• Amlodipine 10 mg po daily
• Colace 100 mg po BID
• Oxycodone 5 mg po q4hr PRN pain
Patient Case

• What are some of the major side effects associated with Mr. HK’s tacrolimus?

  • A: Neurotoxicity (Headache and tremors)
  • B: Hyperpigmentation
  • C: Renal dysfunction
  • D: Glaucoma
  • E: A and C
Patient Case

• 1 year later Mr. HK is readmitted to the hepatology service at VUMC for biopsy proven rejection.

• He was treated with:
  – Methylprednisolone 500 mg IV x 3 doses

• His liver numbers did not respond and remained elevated. Another biopsy was completed showing continued rejection and he was treated again with methylprednisolone 500 mg IV x 3 doses. Unfortunately, his numbers never declined. What antibody should we use to treat the steroid resistant rejection?
  – A: basiliximab
  – B: Second round of methylprednisolone
  – C: alemtuzumab
  – D: anti-thymocyte globulin
Patient Case

• Three weeks later Mr. HK is readmitted to the MICU with tachycardia, hypotension, and fever. He wife states he got sick after working with compost in his garden. He is started on Zosyn, Vancomycin, and Micafugin.

• Mr. HK continues to decompensate and 24 hours later antifungal coverage is broadened to voriconazole to cover for aspergillus.
Patient Case

What do you expect Mr. HK’s tacrolimus level to do with the addition of voriconazole?

– A: Decrease by 25%
– B: Increase by 75%
– C: Stay stable
– D: Decrease by 75%
Patient Case

- After the addition of the voriconazole the following is noted with his tacrolimus levels.

<table>
<thead>
<tr>
<th>Date</th>
<th>Tacrolimus Dose</th>
<th>Tacrolimus Level</th>
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</thead>
<tbody>
<tr>
<td>8/1/13</td>
<td>2 mg BID</td>
<td>&lt;2</td>
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<tr>
<td>8/2/13</td>
<td>Held</td>
<td>10</td>
</tr>
<tr>
<td>8/3</td>
<td>Held</td>
<td>12.8</td>
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<tr>
<td>8/4</td>
<td>Held</td>
<td>10.7</td>
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<tr>
<td>8/5</td>
<td>Held</td>
<td>6.7</td>
</tr>
<tr>
<td>8/6</td>
<td>0.5 mg BID</td>
<td>5.8</td>
</tr>
</tbody>
</table>
References


References