Care for kidney transplant patients: treatment and vaccination guidance

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Presentation Outline

• The post-transplant immunosuppressive regimen for kidney transplant recipients
• Application of generic medications
• Use of vaccines in kidney transplant recipients

Disclosure: no financial relationships to disclose
The Post-Transplant Immunosuppressive Regimen

1. List the most common immunosuppressant medications utilized in the post-transplant regimen and explain the rationale for switching to agents less often used.

Timeline of immunosuppression

- Tacrolimus
- Mycophenolate
- Sirolimus
- Basiliximab
- Daclizumab
- Thymoglobulin
- Generic tacrolimus, MMF
- Belatacept
- OKT3
- Cyclosporine
- ATGAM
- Steroids
- Azathioprine
- Radiation

The Menu of Immunosuppression

| Polyclonal antibodies | • Equine anti-thymocyte globulin (ATGAM)  
|                        | • Rabbit anti-thymocyte globulin (Thymoglobulin) |
| Monoclonal antibodies | • Basiliximab (Simulect) |
| Calcineurin inhibitors | • Cyclosporine: Neoral (modified)  
|                        | • Sandimmune (non-modified)  
|                        | • Tacrolimus |
| Anti-proliferatives   | • Azathioprine (Imuran) and generics  
|                        | • Mycophenolate mofetil (Cellcept)  
|                        | • EC-mycophenolate sodium (myfortic)  
|                        | • Sirolimus (rapamune)  
|                        | • Everolimus (Zostress) |
| Steroids             | • Methylprednisolone (Solu-medrol)  
|                        | • Prednisone (Deltasone) and generics |

Calcineurin Inhibitors

- First line CNI: tacrolimus (2A)
- CNI (tacrolimus (2D) or cyclosporine (2B)) should be started before or at the time of transplantation, rather than delayed until the onset of graft function
Anti-metabolites

Mycophenolate suggested as the first-line antiproliferative agent (2B)

Mammalian Target of Rapamycin Inhibitors (mTORi)

Do not start until graft function is established and surgical wounds are healed (1B)
Corticosteroids

In patients who are at low immunological risk of rejection and who receive induction therapy, corticosteroids could be discontinued during the first week after transplantation (2B)

Induction therapy

- First line induction therapy: Basiliximab (IL2-RA) (1B)
- High immunologic risk: Thymoglobulin (T-cell depleting) (2B)

OPTN/SRTR Annual Data Report. 2015 American Journal of Transplantation 2017; 17 (S1): 1–564
Toxicity Profiles of Immunosuppressive Medications

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Steroids</th>
<th>CsA</th>
<th>Tac</th>
<th>mTOR</th>
<th>MMF</th>
<th>AZA</th>
</tr>
</thead>
<tbody>
<tr>
<td>New-onset diabetes mellitus</td>
<td>↑</td>
<td></td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>↑</td>
<td></td>
<td></td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>↑</td>
<td></td>
<td></td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteopenia</td>
<td>↑↑</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia and leukopenia</td>
<td>↑↑</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed wound healing</td>
<td>↑</td>
<td></td>
<td></td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea, nausea/vomiting</td>
<td>↑</td>
<td></td>
<td></td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>↑</td>
<td></td>
<td></td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased GFR</td>
<td>↑</td>
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<td>↑</td>
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</tr>
</tbody>
</table>


Summary of Immunosuppression

- Tacrolimus and mycophenolate represent the mainstay of immunosuppression used today
- Side effects and tolerability may lead to selection of less commonly used immunosuppressants
Generic Immunosuppressants

2. Explain the role of the pharmacist when counseling patients prescribed generic immunosuppressants

Background

• Between 2008 and 2010, FDA approved several generic formulations
  – Tacrolimus
  – Mycophenolate mofetil

• Can generic medications (tacrolimus) be safely as substitutes for innovative product?
Generics: Definitions and Regulations

- **Pharmaceutical equivalence**: same active ingredient, identical strength, dosage form, and route
- **Bioequivalence**: must reach the systemic circulation at an equivalent rate extent
- **Labeling**
- **Good manufacturing practice regulations**

Concerns with Generic Regulations

- Clinical data not required
- Time to $C_{max}$ or trough concentration ($C_0$) are not assessed or compared
- AB generics are not tested to see if they are bioequivalent to each other
Tacrolimus: Available Generics

Conversion from Brand to Generic

Pre-conversion:
2-5 levels ($C_0$)

Post-conversion:
1-4 levels ($C_0$)

FOLLOW-UP:
4 days - 2.6 months

<table>
<thead>
<tr>
<th>Pre-conversion $C_0$ levels</th>
<th>Post-conversion $C_0$ levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 - 14.3</td>
<td>1.1 - 10.3</td>
</tr>
</tbody>
</table>

Overall: < than 5% change

Venkataramanan R et al. Am J Transplant 2010;10(S4): abstract 1741
Impact of Changing to Generic Formulation

<table>
<thead>
<tr>
<th>Trough level (C₀)</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase &gt; 20%</td>
<td>5</td>
</tr>
<tr>
<td>Any increase</td>
<td>16</td>
</tr>
<tr>
<td>Decrease &gt; 20%</td>
<td>9</td>
</tr>
<tr>
<td>Any decrease</td>
<td>16</td>
</tr>
</tbody>
</table>

- 78% significant variation
- 43% change greater than 20%

No increase in signs or confirmed diagnosis of acute rejection

Venkataramanan R et al. Am J Transplant 2010;10(S4): abstract 1741

Multi-Center Experience

1:1 dose conversion (brand: generic)

Patients (n = 102)
57 ± 51 months post-transplant
Stable tacrolimus dose for at least 4 weeks

Generic Dose Requirements & Cost

Dosage titrations occurred in 29%

<table>
<thead>
<tr>
<th></th>
<th>($) per mo.</th>
<th>($) per avg. life of the graft (8.7 years )</th>
</tr>
</thead>
<tbody>
<tr>
<td>AWP</td>
<td>77</td>
<td>8,105</td>
</tr>
<tr>
<td>Co-pay</td>
<td>19</td>
<td>2,000</td>
</tr>
</tbody>
</table>

Transplantation. 2011; 92(6):653-7

Summary

- Conversion is permissible without any impact on transplant outcomes
- Some will require dose titration

Recommendations for Use of Generics

- Initial dose conversion 1:1
- Notify the transplant center of switch
- Increase oversight during switch
- Therapeutic drug monitoring
  - Increase frequency of monitoring
  - Return to normal monitoring schedule:
    - steady state
    - stable levels
Immunization of Kidney Transplant Recipients

3. Explain current guidelines and recommendations for the vaccination of kidney transplant recipients

4. List the types of vaccines that are contraindicated, discuss the rationale, and explain how to counsel patients and caregivers on the appropriate use of vaccines

5. Describe the differences in the treatment of influenza in the immunosuppressed kidney transplant patient vs. a non-immunocompromised patient

6. Provide counseling to patients and caregivers on the use of vaccines

Immunity

Passive immunity
- Intravenous immunoglobulin

Adaptive immunity
- Vaccination (live or inactive)

*Clinical pearl:* blood products (IVIG) interfere with the response to live vaccines; delay these vaccines for 3 months after receiving blood products

Adapted from: http://keckmedicine.adam.com/content.aspx?productId=617&pid=1&gid=002024
http://www.fragmenthealth.com/galery/blood_transfusion.jpg
## Comparison: Passive vs. Adaptive

### Passive
- Short duration
  - A few weeks
- Effective immediately
- Receipt of non-self antibodies

### Adaptive
- Long duration
  - Lifelong
- Delayed effectiveness
  - May take weeks
- Self production of antibodies

![How Vaccines Work](image-url)

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Pharmacology of Immunosuppression

Induction Immunosuppression

- **Immunosuppressive effects agent dependent**
  - Thymoglobulin vs. Basiliximab
- **Thymoglobulin**
  - T-cell depletion may last for months to years (2 years)

Goal Tacrolimus Levels (ng/mL)

- **Month 0-3**
  - 8-10
  - More intense immunosuppression

- **Month 3-6**
  - 6-8

- **Month 6-12**
  - 6
  - Less intense immunosuppression

Corticosteroids

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Dose (mg)</th>
<th>Post-operative day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylprednisolone</td>
<td>500 mg (in OR)</td>
<td>0</td>
</tr>
<tr>
<td>Prednisone</td>
<td>160</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>5-9</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>10-19</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>20-24</td>
</tr>
<tr>
<td></td>
<td>7.5</td>
<td>25-29</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>30-on</td>
</tr>
</tbody>
</table>
Clinical Concerns

1. Does vaccination increase the risk of transplant rejection?
2. Is the ability to mount an immune response impacted by the amount and/or type of immunosuppression after transplant?
3. What is the optimal time to give vaccines after transplant?


Timeline of Infection After Transplant

Influenza in Transplantation

• Greater risk of morbidity and mortality*

• Cause of allograft dysfunction and acute rejection**
  - Kidney
  - Lung

• Response to the vaccine & effectiveness not well described


Humoral and Cellular Immune Responses after Influenza Vaccination in Kidney Transplant Recipients

| Patients | • 66 kidney transplant recipients (not recent) |
| Control | • 19 healthy individuals |
| Purpose | • Investigate the humoral & cellular response to influenza vaccine  
  • To address the risk of HLA sensitization and/or allograft rejection |
| Outcomes | Anti-influenza antibodies (3 strains)  
  • Positive response: titer > 50 (seroconversion)  
  • 3 fold titer increase  
  • T-cell enzyme-linked immunoSpot (ELISPOT) assay (cellular) influenza specific response  
  • Anti-HLA antibodies (humoral)  
  • Donor specific antibodies (DSA) – linked to rejection |

Positive Vaccine Responses

<table>
<thead>
<tr>
<th>Influenza Strain</th>
<th>Transplant (%)</th>
<th>Healthy (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/H1N1 (unchanged)</td>
<td>10</td>
<td>58</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>A/H3N2 (changed)</td>
<td>22</td>
<td>58</td>
<td>0.004</td>
</tr>
<tr>
<td>B (unchanged)</td>
<td>20</td>
<td>26</td>
<td>&gt; 0.05 NS</td>
</tr>
<tr>
<td>Overall (at least 1 strain)</td>
<td>46</td>
<td>84</td>
<td>0.004</td>
</tr>
</tbody>
</table>

- Response largely due to an ↑ in antibody titers except for H3N2
- Vaccine response significantly lower for A/H1N1 and A/H3N2 in immunosuppressed transplant patients than in healthy controls
- Similar response to B strain

Factors Effecting Response

B. Total proportion of individuals responding to at least one strain (dark bars)
C. Individuals mounting an antibody response toward one, two or three strains
D. Patients +/- MMF according to humoral postvaccinal response
Immunosuppression

- No influence of maintenance immunosuppression
  - Mycophenolate mofetil dose
  - Steroid dose
  - Trough levels of sirolimus or tacrolimus
- Did not assess induction therapy

Influenza Specific T-Cell activity

- Important for viral clearance during ongoing infection
  - Provision of T-helper component of humoral immunity
- Significant response detected in transplant patients
- Included response to major antigens in vaccine
  - Transplant: 13 out of 46 (28%)
  - Control: 3 out of 12 (25%)
    - p > 0.05
- This did not impact antibody response
Donor Specific Antibodies (DSA)

- DSA day 0 (baseline):
  - n = 14 (22%)
    - Class I: n = 5
    - Class II: n = 9
  - All detected at day 30
    - Not significantly changed
    - No enhancement of anti-donor sensitization
    - ↑ in 3 class II DSA with high MFI value (>10,000)

Sensitization after Vaccination

- de novo DSA (day 30): n = 3 (4.8%)
  - Low MFI for all three
    - Patient 1: 482
    - Patient 2: 322
    - Patient 3: 624
Rejection Episodes

- No clinical or biological signs of rejection at 3 months
  - Including those with baseline & de novo DSA
- Serum creatinine:
  - $1.59 \pm 0.77$ mg/dL (day 0)
  - $1.55 \pm 0.58$ mg/dL (day 90)
  - $p > 0.05$


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**Decreased Antibody Response to Influenza Vaccination in Kidney Transplant Recipients: A Prospective Cohort Study**

Kelly A. Birdwell, MD, MSc1, Mine R. Ikizler, MS2, Edith C. Sarinella, MT2, Li Wang, MS3, Daniel W. Byrnes, MS2, T. Alp Ikizler, MD1 and Peter F. Wright, MD1

<table>
<thead>
<tr>
<th>Patients</th>
<th>53 kidney transplant recipients (single center: Vanderbilt University) 36% (19 out of 53) &lt; 6 months post-transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>106 healthy participants</td>
</tr>
<tr>
<td>Purpose</td>
<td>Antibody response to inactivated influenza vaccine is not well described in this population using newer &amp; commonly used immunosuppressive agents</td>
</tr>
<tr>
<td>Hypothesis</td>
<td>Tacrolimus based immunosuppression would result in decreased antibody response compared to healthy controls using 2006-2007 standard trivalent inactivated vaccine</td>
</tr>
</tbody>
</table>
| Outcomes | Primary Proportion of patients achieving:  
  - Seroresponse (4 fold increase in titer)  
  - Seroprotection (antibody titer $> 1:32$)  
  Influenza types: A/H1N1, A/H3N2, B  
  Assessed at 1 month post vaccination  
  Secondary Associations of antibody response with:  
  - Gender  
  - Age  
  - Immunosuppression  
  - Time from transplant  
  - Kidney function (SCr at 1 month) |

Serological Response (antibody titers)

- Post-vaccination titers increased significantly from baseline for all stains in each group
- Mean change (pre vs. post vaccination titers) significantly different between healthy (control) & transplant group for all 3 strains

Other Studies: Immunosuppression

<table>
<thead>
<tr>
<th>Experimental</th>
<th>Control</th>
<th>Findings</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine (CSA)</td>
<td>Azathioprine (AZA)</td>
<td>(CSA) group ↓ antibody response to influenza vaccine</td>
<td>1 &amp; 2</td>
</tr>
<tr>
<td>Cyclosporine (CSA) Mycophenolate (MMF) Prednisone (PRED)</td>
<td>Cyclosporine (CSA) Azathioprine (AZA) Prednisone (PRED)</td>
<td>Transplant patients &lt; 6 months excluded • Similar seroresponse and seroprotection • MMF had effect on vaccine response (H1N1) • Lower probability of protective titers with ↑ PRED doses (A/H1N1) ↑ CSA doses (A/H3N2)</td>
<td>3</td>
</tr>
<tr>
<td>Multiple regimens</td>
<td>Healthy controls</td>
<td>Transplant patients &lt; 6 months excluded • Similar seroresponse and seroprotection • Major impact of MMF (&gt; 2 g) for all viral strains</td>
<td>4</td>
</tr>
</tbody>
</table>

Other Factors Effecting Vaccine Response

• Chronic Kidney Disease
• End Stage Renal Disease (Hemodialysis)
• Type of transplant*


Other Vaccines With Impaired Immunogenicity

• Hepatitis B$^{1,2}$
• HPV$^3$
• Tetanus$^4$
• Varricella$^5$

2. Lefebure AF et al. Vaccine 1993; 11: 397-399
Results Applied to Guidelines & the Practice of Vaccination

Birdwell et al.  
Am J Kidney Dis 54:112-121

- Time post-transplant
- Maintenance immunosuppressants
- Type of strain
- Baseline seroprotection
- Age, gender, and race

Candon S et al.  
A J Transplantation 2009; 9: 2346-54

- Time post-transplant
- Maintenance immunosuppressants
- Sensitization & rejection
- T-cell & humoral response
- New Influenza antigens
- Age, gender

Possible increased susceptibility to influenza in this population despite vaccination

Vaccination Recommendations

- No evidence of allograft rejection (Grading II-2)
- Vaccinate early
  - Document pre-transplant
  - Live vaccines prior to transplant
  - Refer for vaccination at the time of listing
- Vaccinate after transplant
  - 3-6 months post-transplant
  - Inactivated vaccines safe
  - live contraindicated

Adult Recommendations: AST

Live Attenuated Vaccines

- Influenza (LAIV)
- Varicella◊ (Varivax*, Zostavax)
- Measles, Mumps, Rubella (MMR◊)
- BCG (TB)

Inactive vaccines

- Influenza
- Hepatitis A* & B◊
- Pertussis
- Tetanus*
- Inactivated polio
- S. pneumoniae* (Pneumovax23 – polysaccharide & Prevnar13- conjugated)
- N. Meningitidis
- Human papillomavirus (HPV)
- Rabies*

*Monitor titers after vaccination
◊ Check serology prior to transplant: if (–) dose x1 check serology post-vaccination
♠ Delay for 3 months if administered intravenous immunoglobulin (IVIG)


- Prior to planned immunosuppression if feasible (strong, moderate)
- Live vaccines
  - Administer ≥ 4 weeks prior to immunosuppression (strong, low)
  - Avoid within 2 weeks of initiation of immunosuppression (strong, low)
- Inactive vaccines
  - Administer ≥ 2 week prior to immunosuppression (strong, moderate)

Clinical infectious disease (CID) 2014; 58: e44-e100
CMS Recommendations: Influenza

- Not vaccinating may leave a transplant recipient vulnerable to infection
- All patients (including transplant) should be immunized prior to discharge
- Immunization very early post-transplant
  - Decreased immune response to the vaccine

Antiviral Prophylaxis

Oseltamivir 75 mg daily for 12 weeks

*Use when vaccine is contraindicated or patient may have insufficient response; start at the beginning of influenza season* (grade I)

*If live attenuated vaccine administered inadvertently: anti-viral therapy and subsequent revaccination with inactivated vaccine can be considered* (grade III)

Oseltamivir Treatment Considerations

• Prolonged viral replication in transplant patients
  – Extend course beyond 5 days to 10-14 days
  – Viral replication (PCR) may guide duration of therapy
• Dosing during severe cases
  – Doubling of the dose sometimes recommended
    • 150 mg twice daily (normal kidney function)
• Renal dosing recommendations vary (CrCl <30 ml/min):
  – Drug information database: 30 mg once daily
  – Guidelines and package insert: 75 mg once daily
• No clinically relevant interactions with immunosuppressants

Khana N et al. Transplant Infect Dis 2009; 11: 100-105
Lam et al. Ther Drug Monit 2011; 33: 699-704
Tamiflu (oseltamivir) [prescribing information]. South San Francisco, CA: Genentech, Inc; June 2016.

Household Contacts

• Family members should be fully vaccinated
  o Influenza vaccine yearly (inactive preferred)
• Live vaccines if it is the only option
  o Measles, mumps, rubella, and varicella
  o Except: oral polio and small pox
• Live attenuated influenza vaccine (LAIV) & Rotavirus
  o Good use of infection prevention
Counseling Patients

- They are safe, effective, & important to outcomes
- You may have reduced response to vaccines
- Local pharmacies can increase access to vaccination
- Ensure that you and your family members are properly vaccinated after your transplant
- Take extra precaution during flu season

Pets

- Pets should be fully immunized
  - Little or no risk of transmission following immunization of pets with live vaccines
  - (canine bordetella bronchiseptica intranasal)
Unanswered Questions & Prospective Research

• Immunosuppression
• Chronic Kidney Disease
• Impact of new viral strains
• Strategies for early vaccination (i.e. booster)
• Cost effectiveness of early vaccination
• Study Design
• Outcomes

Care for kidney transplant patients: treatment and vaccination guidance

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