Immunology/Transplantation PRN Focus Session—Novel Approaches to Immunomodulation After Transplantation

Activity Number: 0217-0000-15-129-L01-P, 1.50 hours of CPE credit; Activity Type: A Knowledge-Based Activity

Monday, October 19, 2015
3:15 p.m. to 4:45 p.m.
Plaza Room B

Moderator: Christopher R. Ensor, Pharm.D., BCPS
Assistant Professor of Pharmacy and Therapeutics, University of Pittsburgh School of Pharmacy, Pittsburgh, Pennsylvania

Moderator: Reed Hall, Pharm.D., BCPS
Clinical Pharmacy Specialist, UT Health Sciences Center, San Antonio, Texas

Agenda

3:15 p.m.  Extending Immunosuppression: Once Daily Tacrolimus
Patricia West-Thielke, Pharm.D., BCPS
Assistant Director of Transplant Research, University of Illinois at Chicago, Chicago, Illinois

3:35 p.m.  Belatacept: Beyond De-Novo Renal Transplantation
Rita R. Alloway, Pharm.D., FCCP, BCPS
Research Professor, Director, Transplant Clinical Research, University of Cincinnati, Cincinnati, Ohio

3:55 p.m.  Finding a ‘Home’ for mTOR Inhibitors
Matthew J. Everly, Pharm.D., BCPS
Interim Director, Terasaki Research Institute, Los Angeles and Adjunct Assistant Professor of Medicine, Nephrology Division, David Geffen School of Medicine, University of California, Los Angeles, California

4:15 p.m.  The Future of Immunosuppression is Now!
Jennifer Trofe-Clark, Pharm.D., FCCP, FAST, BCPS
Adjunct Associate Professor of Medicine, Renal Electrolyte and Hypertension Division, Perelman School of Medicine, University of Pennsylvania; Kidney Transplant Clinical Pharmacy Specialist, Department of Pharmacy Services, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

4:35 p.m.  Panel Discussion

Conflict of Interest Disclosures

Rita R. Alloway: Consultant/member of advisory board for Veloxis Pharmaceuticals, Astellas, Sanofi, and Amgen; Speaker’s bureau for Sanofi.
Christopher R. Ensor: no information provided.
Matthew J. Everly: no conflicts to disclose.
Reed Hall: no conflicts to disclose.
Jennifer Trofe-Clark: Clinical investigator for Veloxis Pharmaceuticals and Agency for Healthcare Research and Quality; Received grant funding for Veloxis Pharmaceuticals and Agency for Healthcare Research and Quality.
Patricia West-Thielke: Received grant funding for Veloxis Pharmaceuticals and Astellas.

Learning Objectives

1. Evaluate the pharmacokinetics and clinical utility of novel once daily tacrolimus formulations.
2. Compare and contrast the two available once daily tacrolimus formulations.
3. Recognize the evolving role of belatacept in transplant immunosuppression.
4. Design a transplant immunosuppression regimen incorporating the non-traditional use of belatacept.
5. Distinguish the role for mammalian target of rapamycin (mTOR) inhibitors in transplant recipients.
6. Describe the pros and cons of mTOR inhibitor use for transplant immunosuppression.
7. Discuss the future of immunosuppression management, including pharmacogenomic assessments.
8. Describe the transplant immunosuppression pipeline opportunities and challenges.

Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/gc15.
Extending Immunosuppression: Once Daily Tacrolimus

Patricia M. West-Thielke, PharmD, BCPS
Director of Clinical Research
University of Illinois Health
Department of Surgery

Objectives
• Evaluate the pharmacokinetics and clinical utility of novel once daily tacrolimus formulations
• Compare and contrast the two available once daily tacrolimus formulations

PK Background
• Bioavailability - % of the total dose administered that is absorbed and available in the circulation
• Bioequivalence – the absence of a significant difference in the bioavailability of 2 drugs administered at the same dose
• Narrow therapeutic index drug – a drug with a narrow therapeutic range = tacrolimus

PK background
• AUC, Cmax, Cmin – we are all familiar with these
• Measures of variation:
  – Fluctuation → 100x(Cmax-Cmin/Cavg); peak trough exposure normalized to average concentration
  – Swing → 100x(Cmax-Cmin/Cmin); peak trough exposure normalized to trough

Tacrolimus Formulations
• Three branded formulations are currently available on the market:
  • Once-daily Envarsus XR
    • Approved July 10, 2015
    • 80% reduction in dose from immediate release
  • Once-daily Astagraf XL
    • Approved July 19, 2013
    • 1:1 conversion with immediate release
  • Twice-daily Prograf or generic – immediate release

Conflict of Interests
• Received grant funding for Veloxis Pharmaceuticals and Astellas.
Astagraf

• Extended-release formulation of tacrolimus
  – Tacrolimus is mixed with ethylcellulose, hypromellose and lactose to form immediate-sustained-release granules
  – Ethylcellulose controls the rate of permeation of water into the granules giving it the sustained release character
• Similar safety and non-inferior efficacy vs. twice-daily tacrolimus capsules (Prograf)

Envarsus XR

• Utilizes MeltDose technology to reduce the size of the drug particles to individual molecules
  – Creates a solid dispersion, or “solid solution,” of the drug
  – A patented nozzle sprays the drug onto a carrier which becomes a granulate which is then compressed into tablets
• Delivers the tacrolimus throughout the GI tract → stable consistent absorption over the whole day
  – ↑ bioavailability, ↓ peak, ↓ peak-to-trough fluctuation
• Similar safety and non-inferior efficacy vs. twice-daily tacrolimus capsules (Prograf)

ASTCOFF

• ASTCOFF is an open label, randomized, crossover study
• Stable renal transplant recipients were randomized to receive Prograf for one week and then either
  • Envarsus for one week then Astagraf for one week or
  • Astagraf for one week then Envarsus for one week
• Conversion factor of 1:1:0.80mg (Prograf:Astagraf:Envarsus)
• Tacrolimus levels analyzed by tandem mass spectrometry
• No dose titrations were allowed (MMF, prednisone, tacrolimus)
• 24-hour PK collections performed at the end of one-week periods

Results

• Thirty-one patients were randomly assigned to and dosed with study drug
  – 16 in Prograf:Envarsus:Astagraf
  – 15 in Prograf:Astagraf:Envarsus
• Baseline characteristics were similar across the groups
  – P → E → A vs. P → A → E
    • Mean age 50.1 vs 46.3 years;
    • 56 vs 60% male;
    • 81.3 vs 66.7% Caucasian

<table>
<thead>
<tr>
<th>Observed PK Parameters and Summary Comparisons Between Tacrolimus Formulations</th>
</tr>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Total daily dose [mg]</td>
</tr>
<tr>
<td>AUC_{24} [hr*ng/mL]</td>
</tr>
<tr>
<td>C_{max} [ng/mL]</td>
</tr>
<tr>
<td>C_{min} [ng/mL]</td>
</tr>
</tbody>
</table>

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Results

Observed Pharmacokinetic Profile

Mean +/- SE (ng/mL) Time (hr) since AM dose

<table>
<thead>
<tr>
<th></th>
<th>Astagraf</th>
<th>Envarsus</th>
<th>Prograf</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC24 (hr*ng/mL) [geometric mean]</td>
<td>102.4 (94.4, 111.1)</td>
<td>100.6 (92.7, 109.1)</td>
<td>100.6 (91.3, 110.8)</td>
</tr>
<tr>
<td>Cmax (ng/mL) [geometric mean]</td>
<td>82.8 (75.1, 91.4)</td>
<td>99.2 (89.9, 109.4)</td>
<td>82.5 (73.9, 92.0)</td>
</tr>
<tr>
<td>Cmin (ng/mL) [geometric mean]</td>
<td>93.6 (85.4, 102.6)</td>
<td>89.6 (81.8, 98.2)</td>
<td>103.1 (93.9, 113.2)</td>
</tr>
</tbody>
</table>

Results

Exposure-Normalized PK parameters

<table>
<thead>
<tr>
<th></th>
<th>Ratio of Geometric Means, RGM [90% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/P</td>
<td>102.4/100.6 (94.4/92.7, 111.1/109.1)</td>
</tr>
<tr>
<td>A/P</td>
<td>100.6/100.6 (92.7/91.3, 109.1/110.8)</td>
</tr>
<tr>
<td>E/A</td>
<td>100.6/100.6 (91.3/91.3, 110.8/110.8)</td>
</tr>
</tbody>
</table>

Results

• Observed data
  • Envarsus presents a flatter PK profile than Astagraf and Prograf respectively
    - ↓ 30% intra-day peak-to-trough fluctuations (p=0.004 and <0.001)
    - ↑ median time to maximal concentration (Tmax) to 6 hours for Envarsus compared to 1.93 hour and 1.48 hour (p<0.001)
    - Conversion strategy used yielded 17% ↑ exposure for Envarsus vs Prograf (p=0.002) and 25.7% higher exposure vs Astagraf (p=0.001)
    - Astagraf provided non statistically significantly ↓ (6.9%) exposure vs Prograf (p=0.149)
• Data normalized to Prograf exposure (AUC) data
  • When normalized to Prograf exposure, Envarsus ↓ Cmax by ~17% when compared to Astagraf and Prograf (p=0.006 and p=0.002, respectively)
  • When normalized to Prograf exposure, Astagraf had similar Cmax and Tmax to Prograf (p=0.887)

Take Home Points from ASTCOFF

• Envarsus PK parameters tended to differ significantly from Astagraf and Prograf, while Astagraf and Prograf tended to be similar to each other.
• Dose conversion analysis supports the following recommended total daily dose conversions rates.
  - Prograf : Astagraf + 8%
  - Prograf : Envarsus -30%
  - Astagraf : Envarsus -36%
  - Significant PK differences between tacrolimus formulations ➔ the formulations are NOT interchangeable or substitutable.

Questions?
Belatacept: Beyond De-Novo Renal Transplantation
Rita R. Alloway, PharmD, FCCP
Research Professor of Medicine
Director, Transplant Clinical Research
University of Cincinnati

2015 ACCP Global Conference on Clinical Pharmacy

Learning Objectives

- Recognize the evolving role of belatacept in transplantation immunosuppression
- Design a transplant immunosuppression regimen incorporating the non-traditional use of belatacept

Belatacept Current Role

- First FDA approved CNI free regimen
  - Approved combination with basiliximab induction, mycophenolate mofetil [MMF], and corticosteroids in adult kidney transplants based upon 1 yr non-inferiority endpoint

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BELA n=226</th>
<th>CYA n=221</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy Failure Month 36 Components</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPAR</td>
<td>68 (25.7)</td>
<td>57 (25.8)</td>
</tr>
<tr>
<td>Graft loss</td>
<td>9 (4.0)</td>
<td>10 (4.5)</td>
</tr>
<tr>
<td>Death</td>
<td>10 (4.4)</td>
<td>15 (6.8)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>2 (0.9)</td>
<td>5 (2.3)</td>
</tr>
</tbody>
</table>

Belatacept Cochrane Review

- No evidence of any difference in the effectiveness of belatacept and CNI in preventing acute rejection, graft loss and death.
- Belatacept is associated with
  - Less chronic kidney scarring and better kidney transplant function
  - Better blood pressure and lipid profile
  - Lower incidence of diabetes versus treatment with a CNI
  - Harms related to PTLD remain unclear
  - Longer-term studies comparing belatacept versus tacrolimus are needed to help clinicians decide which patients might benefit most

Conflict of Interests

- I have financial relationships with BMS as an investigator and Director Coordinating Center
- I have financial relationships within the last 12 mo
  - Clinical Research Grants - Novartis, Astellas, Veloxis, Takeda, Onyx, GSK, Prolong, Bristol-Myers Squibb, Chiltern, Sanofi, and FDA
  - Advisory Board - Veloxis, Astellas, Sanofi, Amgen
  - Speakers Bureau - Sanofi
- This presentation DOES include discussion of off-label use
- ACCP provided travel support
Evolving Role of Belatacept

- Phase 3 study regulatory limitations required concomitant and control immunosuppression that was outdated.
- Detriments to rapid clinical uptake include
  - Increase rate and severity of acute rejection episodes
  - Annual costs of belatacept based regimen compared to generic alternatives is cost prohibitive for many
  - REMS
  - Lack of pediatric use due to EBV black box
  - Lack of available infusion sites willing to accept risks

Rita Alloway, Personal communication

Combination regimens which reduce rate and severity of acute rejection
- T-cell depleting induction
- Alternative combinations with tacrolimus, mTor, etc.
- Alternative regimen various CNI toxicities or diagnoses
- Bridging regimens during DGF or AKI
- Conversion for chronic CNI nephrotoxicity
- Conversion for acute or chronic neurotoxicity, seizure, tremors, posterior reversible encephalopathy syndrome (PRES)
- Recurrent disease
- Thrombotic microangiopathy
- Non renal transplant uses, ie OLT, VCA, panc, etc

Learning Objective 2

- Design a transplant immunosuppression regimen incorporating the non-traditional use of belatacept

WHY????

Belatacept – Denovo
Simultaneous CNI and Steroid Withdrawal

<table>
<thead>
<tr>
<th>Design</th>
<th>Prospective, open label, multi-center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Low moderate immunologic risk</td>
</tr>
<tr>
<td></td>
<td>EBV recipients seropositive</td>
</tr>
<tr>
<td>Intervention</td>
<td>Antithymocyte globulin (rabbit) 1.5mg/kg x 4, Bela, MPA, CSWD</td>
</tr>
<tr>
<td></td>
<td>Antithymocyte globulin (rabbit) 1.5mg/kg x 4, Siro, MPA, CSWD</td>
</tr>
<tr>
<td>Comparator</td>
<td>Antithymocyte globulin (rabbit) 1.5mg/kg x 4, Tacrolimus, MPA, CSWD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes of Interest</th>
<th>Variable</th>
<th>Bela (n=33)</th>
<th>Siro (n=36)</th>
<th>Tacro (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPAR</td>
<td></td>
<td>12%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Graft Survival</td>
<td></td>
<td>94%</td>
<td>92%</td>
<td>100%</td>
</tr>
<tr>
<td>Patient Survival</td>
<td></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Mean eGFR (1yr/4yr)</td>
<td>64/60</td>
<td>62/72</td>
<td>54/56</td>
<td></td>
</tr>
</tbody>
</table>


Belatacept – Denovo

Design          | Prospective, single center |
Population      | 12 kidney transplants (cPRA 0%) |
                 | EBV recipients seropositive |
Intervention    | Antithymocyte globulin 2-5mg/kg, 5-7 doses |
                 | Enteric coated MPA |
                 | Chronic steroids |
Comparator      | None, Proof-of-concept |

Outcomes of Interest
- 2/12 acute rejection treated with steroids
- 6/12 infections with 5 pts admitted
- No PTLD
- 100% patient and graft survival (6mos)
- Good renal function


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Belatacept – Denovo

**Design**
Prospective, randomized, multi-center

**Population**
- 315 kidney transplants
- cPRA <25%
- EBV recipient seropositive

**Intervention**
- Belatacept 10mg/kg @ POD 1, 5, 15, 28, 56, 84, then 5mg/kg monthly
- OR
- Tacrolimus targets POD 0-30 8-12ng/mL, >30 5-10ng/mL

**Comparator**
- Antithymocyte globulin(rabbit) 4-6mg/kg OR alemtuzumab 30mg x 1 dose

**Ampa**
CSWD at 5 days

**Outcomes of Interest**
- Renal function >45ml/min
- Patient and Graft Survival
- Rate, Type and Severity of Rejection

Belatacept – Conversion

**If immediate CNI discontinuation, initiate bela at denovo dosing.**

**If patient is switched to bela**
- Belatacept 5 mg/kg IV on days 1, 15, 29, 43, and 57, and then every 28 days thereafter.
- CNI dose was tapered as follows:
  - 100% on day 1,
  - 40 to 60% on day 15,
  - 20 to 30% on day 23, and
  - none on day 29 and beyond.

Belatacept – Monitoring

**Upper limit of therapeutic window defined, but not lower limit**

**PK and PD (CD86-saturation) markers have limited interpatient variability**

**No commercially available monitoring assay**

**Authors state TDM may not be necessary, except to minimize adverse events**

**TDM needed to monitor patients with viral infections and potentially breakthrough rejections**

Belatacept – Denovo

**University of Cincinnati Sponsor and Coordinating Center**

**218 out of 315 enrolled**

**DSMB has allowed enrollment to continue based upon 150pts enrolled with 2 months followup**

**FDA IND precludes reporting any results by group until enrollment complete**

Belatacept – Denovo

**Clinical Pearls - Efficacy**
- Expect lower baseline SrCr values thus recalibrate your trigger for biopsy
- Consider treating steroids resistant rejections with high dose tacrolimus
- Continue belatacept when treating rejection with tacrolimus
- Maintain MPA at target AUCs
- Once baseline SrCr achieved, do NOT expect “creatinine creep”
- Diagnosis of rejection does NOT require tacrolimus maintenance conversion

Belatacept – Denovo

**Clinical Pearls - Toxicity**
- Monitor MPA AUCs, may witness supratherapeutic MPA AUCs in tacrolimus, steroid free regimen.
- Dose adjust MPA, but tolerate absolute neutrophil counts = 1500, if stable.
- Aggressively dose decrease MPA in cases of viral infections, ie CMV, BKV, etc.
- If no response in viral titers, discontinue MPA.
- If no response, may extend belatacept dosing interval.

Belatacept – Denovo

**Clinical Pearls - Efficacy**

- University of Cincinnati Sponsor and Coordinating Center
- 218 out of 315 enrolled
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Belatacept – Denovo

**Clinical Pearls - Toxicity**

- Monitor MPA AUCs, may witness supratherapeutic MPA AUCs in tacrolimus, steroid free regimen.
- Dose adjust MPA, but tolerate absolute neutrophil counts = 1500, if stable.
- Aggressively dose decrease MPA in cases of viral infections, ie CMV, BKV, etc.
- If no response in viral titers, discontinue MPA.
- If no response, may extend belatacept dosing interval.
Future Directions

- True pharmacoeconomic evaluation is complex
  - Multiplicity of payors over the lifetime of a transplanted graft
  - Evaluating drug costs in the context of potential savings
    - Lab costs, coordinator time, extended graft and patient survival, etc
- Ease administration
  - Facilitate administration via home infusion
  - Unlimited infusion centers
  - Expand label or allow for off-label uses
- True adherence known

Questions?

Rita R. Alloway, PharmD, FCCP
Research Professor of Medicine
University of Cincinnati
Office: 513.558.1568
Rita.alloway@uc.edu
Learning Objectives

- Distinguish the role for mammalian target of rapamycin (mTOR) inhibitors in transplant recipients.
- Describe the pros and cons of mTOR inhibitor use for transplant immunosuppression.

Bringing mTOR inhibitors to transplantation

1993: tacrolimus
1983: Cyclosporine

- Improved 1 year survival rates to 90%
- Improved 1-year acute rejection rates to less than 20%
- Did not improve long term allograft survival
- Calcineurin inhibitor nephrotoxicity
- Lack of impact on B-cell/humoral rejection

Preventing early acute rejection does not dramatically impact long term outcomes

Hypothesis:
Calcineurin inhibitors hinder long-term allograft function

CNI withdrawal & conversion studies

<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>Intervention arm</th>
<th>Control arm</th>
<th>CNI stopping strategy</th>
<th>Study length (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>SRL, Tacrolimus 40 mg</td>
<td>SRL, Tacrolimus 40 mg</td>
<td>Conversion to Tacrolimus 40 mg</td>
<td>12 months</td>
</tr>
<tr>
<td>2019</td>
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<td>SRL, Tacrolimus 40 mg</td>
<td>Conversion to Tacrolimus 40 mg</td>
<td>12 months</td>
</tr>
<tr>
<td>2020</td>
<td>SRL, Tacrolimus 40 mg</td>
<td>SRL, Tacrolimus 40 mg</td>
<td>Conversion to Tacrolimus 40 mg</td>
<td>12 months</td>
</tr>
<tr>
<td>2021</td>
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<td>SRL, Tacrolimus 40 mg</td>
<td>Conversion to Tacrolimus 40 mg</td>
<td>12 months</td>
</tr>
</tbody>
</table>

CNI avoidance studies

<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>Drug</th>
<th>Dose (mg)</th>
<th>Renal survival</th>
<th>Graft survival</th>
<th>Death of patient</th>
<th>Rejection rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>Tacrolimus</td>
<td>20 mg</td>
<td>90%</td>
<td>90%</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>2019</td>
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<td>90%</td>
<td>90%</td>
</tr>
</tbody>
</table>

HERA and other CNI withdrawal & conversion studies

- Early conversion could be seen as efficacious from the collective trials.
- However, higher acute rejection rates, appearing just after conversion, and adverse events to mTOR inhibitor were a problem.
Table 1

<table>
<thead>
<tr>
<th>Transplantation 2009; 87:233.</th>
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</thead>
</table>

Conversion From Calcineurin Inhibitors to Sirolimus Maintenance Therapy in Renal Allograft Recipients: 24-Month Efficacy and Safety Results From the CONVERT Trial

|------------------------------------------------|

Donor-Specific HLA Antibodies in a Cohort Comparing Everolimus With Cyclosporine After Kidney Transplantation

|------------------------------------------------|

Conversion From Calcineurin Inhibitors to Sirolimus Maintenance Therapy in Renal Allograft Recipients: 24-Month Efficacy and Safety Results From the CONVERT Trial

|------------------------------------------------|

Everolimus trials: ZEUS sub-study and CRAD001ADE13 sub-study


Table 9

<table>
<thead>
<tr>
<th>Commons after T cells in patients randomized to receive cyclosporine- or everolimus-based immunosuppression</th>
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</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>Retent survival 1%</td>
</tr>
<tr>
<td>DTH responded</td>
</tr>
<tr>
<td>DTH not responded</td>
</tr>
<tr>
<td>Cytokine profile</td>
</tr>
<tr>
<td>Prostate at 6 months</td>
</tr>
<tr>
<td>Prostate at 12 months</td>
</tr>
<tr>
<td>Prostate at 24 months</td>
</tr>
<tr>
<td>Prostate at 36 months</td>
</tr>
<tr>
<td>Prostate at 48 months</td>
</tr>
<tr>
<td>Prostate at 60 months</td>
</tr>
</tbody>
</table>


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5-Year Actual Post- de novo DSA Survival

### Probability of Allograft Survival

- **Years after DSA Appearance**
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5

#### Number at risk
- 59
- 53
- 45
- 33
- 29
- 22

**Everly et al. Transplantation 2013;95:410**


#### What is the “home” for mTOR inhibitors?

- **mTOR and malignancy**
  - **Guba et al. Transplantation 2004;77:1771**

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**The immunosuppressive macrolide RAD inhibits growth of human Epstein–Barr virus-transformed B lymphocytes in vitro and in vivo: A potential approach to prevention and treatment of posttransplant lymphoproliferative disorders**

- **Majewski et al. PNAS 2000;97:4285**

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**Low Incidence of Malignancy among Sirolimus/ Cyclosporine-Treated Renal Transplant Recipients**

- **Majewski et al. PNAS 2000;97:4285**

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mTOR in malignancy:
• Conversion from CNI to mTOR inhibitor may have a lower rate of malignancy development
• May be most beneficial in patients at risk of skin cancer development

Regression of Left Ventricular Hypertrophy in Kidney Transplant Recipients: The Potential Role for Inhibition of Mammalian Target of Rapamycin
E. Paciotti and G. Cannella

Summary
1. CNI-free, mTOR inhibitor based regimens have higher rates of rejection

2. More information is needed regarding donor specific antibodies with mTOR inhibition

3. Conversion to mTOR late post-transplant is not recommended in those with poor renal function and/or proteinuria

4. The benefit of mTOR-inhibitor based regimen in renal transplant is reduced CNI nephrotoxicity and a lower incidence of malignancy

5. Greatest renal transplant function benefit from mTOR conversion in 1-6 months

Thank You
meverly@terasakilab.org
Learning Objectives

- Discuss the future of immunosuppression management, including pharmacogenomic assessments
- Describe the transplant immunosuppression pipeline opportunities and challenges

Pharmacogenomic Challenges in Transplant

- Limited implementation of pharmacogenomics in transplant practices to date
  - Lack of strong data supporting improved outcomes with pre-emptive testing
- Timing of sample
  - Obtain at evaluation visit or transplant admission?
    - Consider lab availability and turn-around time for results

Conflict of Interests

- Veloxis Pharmaceuticals where institution received grant/funding research support (co-PI)
- Agency for Healthcare Research and Quality where institution received grant/funding research support (clinical investigator)
- NIH/NIAID/Immune Tolerance Network funded research where institution received grant funding/research support (regulatory coordinator)
- ACCP assistance to attend this meeting

Learning Objective 1

- Discuss the future of immunosuppression management, including pharmacogenomic assessments
Question 1 for the Audience

- Please answer yes or no using your participant response cards.

- Are you familiar with the ASHP Statement on the Pharmacist’s Role in Clinical Pharmacogenomics?

ASHP Statement: Pharmacist's Role in Clinical Pharmacogenomics

- Pharmacist’s Responsibilities
  - Promote optimal use and time of testing
  - Interpret results
  - Educate health care providers, patients and public

- Pharmacist’s Functions
  - All pharmacists should have basic pharmacogenomics understanding


Question 2 for the Audience

- Do you know which of the following transplant immunosuppressants has Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines associated with it?

  - A. Cyclosporine
  - B. Sirolimus
  - C. Tacrolimus
  - D. Belatacept

CPIC Guidelines: CYP3A5 genotyping and tacrolimus


ASERTAA Trial Results

- Tacrolimus clearance [CL/F (L/hr)] = 48.9 L/hr x [(1.33, if days less than 9 post-transplant) x (0.628, if CYP3A5*3/*3 or CYP3A5*3/*7 genotype) or (0.866, if CYP3A5*1/*3 or CYP3A5*1/*6 or CYP3A5*1/*7 genotype) x (1.24, if receiving a steroid) x (1.26 if recipient age between 18-25 yrs)]

- Tacrolimus dose to achieve any given trough calculated by: total daily dose = CL/F x trough goal x 24 hrs /1000

Pharmacogenomics and Immunosuppression

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>CYP3A5 expressers: increase dose recommended</td>
</tr>
<tr>
<td></td>
<td>Other gene polymorphisms of unknown significance</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Genotype guided dosing not recommended</td>
</tr>
<tr>
<td>M-TOR inhibitors</td>
<td>Genotype guided dosing not recommended</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Determine TPMT status prior to therapy initiation</td>
</tr>
<tr>
<td>Mycophenolic Acid Products</td>
<td>Genotype guided dosing not recommended yet</td>
</tr>
<tr>
<td>Belatacept</td>
<td>No information available on genotype guided dosing</td>
</tr>
</tbody>
</table>

Future Pharmacogenomic Directions

- Develop novel approaches to examine the interaction of genetic polymorphisms involved in drug metabolism with transporter proteins and drug mechanisms
- Further define the role of pharmacogenomic donor/recipient variations

Learning Objective 2

- Describe the transplant immunosuppression pipeline opportunities and challenges

Immunosuppressive Pipeline Challenges

- Mainstay of immunosuppression in 2015 is…
  - Drugs developed 15 or more years ago!
- By search criteria “new drugs with immune targets”
  - 436 trials are registered with ClinicalTrials.Gov
    - Less than 20% are being investigated in transplant

Immunosuppressive Pipeline Opportunities

- Off label use of approved agents
  - Anti-rejection agents approved for use in select transplant populations
  - Drugs approved for alternative indications
    - Alemtuzumab, rituximab, bortezomib, eculizumab
- New formulations of existing immunosuppressants
  - Modified cyclosporine, tacrolimus extended release capsules, enteric coated mycophenolic acid and tacrolimus extended release tablets

Question 3 for the Audience

- Please answer true or false using your participant response cards.
- All immunosuppressants that are FDA approved to prevent rejection are approved to be used in all organ transplant populations
Immunosuppression Current Clinical Trial Endpoints

- Composite efficacy endpoint for short term outcomes
  - Rejection, graft, and patient survival at one year
- Non-inferiority versus superiority to current standard of care
- Long term clinical trial feasibility limited

Immunosuppression Clinical Trial Endpoints for the Future

- Validated immunologic profiling, monitoring, genomics
- Measurement of reduction in metabolic complications
- Preservation of graft function in addition to prevention of rejection in kidney transplant recipients
- Patient-reported outcomes

Words of Wisdom from a Transplant Pharmacy Mentor

- If anyone ever questions the value of clinical research, ask the patient.
- When you get frustrated, remember the patient.