Suboptimal Immunosuppression and the Impact on Long Term Graft Loss

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Disclosures

I have financial relationships within the last 12 months with:

Clinical Research Grants
  – Novartis, Astellas, Veloxis, Takeda, Onyx, GSK, Prolong, Bristol-Myers Squibb, Chimerix, Sanofi, and FDA

Advisory Board
  – Veloxis, Astellas, Sanofi, Amgen

Speakers Bureau
  – Sanofi

This presentation does not include discussion of off-label or investigational use of any drugs
Objectives

• Discuss causes and effects of suboptimal immunosuppression (IS) on graft/patient outcomes
  – Iatrogenic IS reductions
  – Non-adherence with prescribed regimen

• Evaluate alternative surrogate clinical endpoints
  – Drug toxicity
  – Tacrolimus variability

• Identify strategies to improve non adherence
Choosing an IS regimen

• Immunologic Factors
  – HLA mismatches, PRA, DSA, race

• Donor Factors
  – Kidney Donor Profile Index (KDPI), ischemic injury

• Patient Comorbidities
  – Viral serologies, malignancy and infectious histories

• Side Effect Profile
  – NODAT, renal, GI, metabolic toxicities

• Personal Experience
IS Regimens after Kidney Transplant

USRDS 2013 annual report, USRDS 2014 annual report-no change
Observations

• Most common IS regimen after kidney transplant:
  – NOT changed over past 10 years
  – NOT labeled for use in kidney transplant
  – Little individualization of IS at 1 year with other agents

• T-cell depleting induction:
  – Anti-thymocyte globulin or alemtuzumab

• 1/3 of patients are steroid-free initially and at 1 year

• Lack of FDA approval of most common regimen:
  – Phase 3 studies: non-inferior design with a regimen used in <25% kidney transplant recipients
  – ↑ Phase 4 costs for testing against standard of care
Iatrogenic IS Minimization: Why?

• Current regimens are suboptimal in promoting long-term graft AND patient survival

• Current challenges
  – Metabolic/cardiovascular complications
    • Corticosteroid withdrawal regimens
  – Calcineurin-inhibitor (CNI) toxicities (nephrotoxicity, etc)
    • Calcineurin inhibitor minimization regimens
    • Calcineurin inhibitor avoidance/conversion regimens
  – Long-term impact of IS (cancer, infection)
    • Overall IS minimization
    • No marker of overall IS
CNI Nephrotoxicity Avoidance Trials

A. Prevalence (%) of various types of rejection over years after transplantation.

B. Cumulative prevalence of CNI nephrotoxicity (%).

CNI Minimization
- SYMPHONY
- ASSET
- OPTICEPT

CNI Elimination
- CAESAR
- ORION
- CENTRAL
- CONVERT
- ZEUS
- Spare the Nephron
- HERAKLES

CNI Avoidance
- SYMPHONY
- ORION
- BENEFIT
- BENEFIT-EXT
CNI Nephrotoxicity Avoidance Trials

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CNI Nephrotoxicity Avoidance Trials

• Effective and safe in some patients

• Effect on renal function
  – Earlier conversion optimal
  – Late CNI withdrawal benefits debatable
  – Clinical benefits of small incremental improvements questioned
  – Agents with larger incremental improvements difficult to obtain

• High discontinuation rates

• ↑ donor-specific antibody production?
  – Impact and late graft loss unknown
Iatrogenic IS Minimization: Thoughts

- Tacrolimus, mycophenolate, and steroids excellent short term outcomes with current endpoints
- Inability to individualize IS minimization
- Lack of mechanistic approach to treat rejection
- Lower limit thresholds of minimization are unknown, and currently present only after damage i.e. rejection or donor specific antibody
Iatrogenic IS Minimization due to Toxicity

**DRUG TOXICITY**

**ON TARGET EFFECTS**
are exaggerations of desired pharmacologic action

**OFF TARGET EFFECTS**
occur when drug interacts with unintended targets

<table>
<thead>
<tr>
<th>On target toxicity</th>
<th>Drug</th>
<th>Off target toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>diabetes, infections</td>
<td>Tacrolimus</td>
<td>vasoreactive nephrotoxicity(both)?</td>
</tr>
<tr>
<td>leukopenia, GI toxicity</td>
<td>Mycophenolate</td>
<td></td>
</tr>
<tr>
<td>anemia, infections</td>
<td>Sirolimus</td>
<td>hypercholesterolemia?</td>
</tr>
<tr>
<td>PTLD</td>
<td>Belatacept</td>
<td>None</td>
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*Limited options to minimize toxicity when toxicity is an “on target” effect*
Toxicity as a Clinical Endpoint

• IS toxicity:
  – Encourages IS minimization?
  – Impacts non-adherence

• Can toxicity be reliably quantitated?

• Can toxicities be differentiated from
  – Comorbid conditions
  – Overall immunosuppressive regimen

• Toxicity as a CLINICAL ENDPOINT
  – A characteristic or variable that reflects how a patient feels, functions, or survives
Patient-Driven IS Minimization: Non-Adherence

Five Dimensions of Adherence

- Health system/HCT-factors
- Social/economic factors
- Condition-related factors
- Therapy-related factors
- Patient-related factors
Patient-Driven IS Minimization: Non-Adherence

Younger Patient
Male Gender
Non Caucasian
Non US resident
Poor social support
Poor transportation
Literacy

Health system/ HCT-factors
Social/economic factors
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Patient-Driven IS Minimization: Non-Adherence

Transplantation 2007:83:858-873
American College of Preventative Medicine
Patient-Driven IS Minimization: Non-Adherence

History of non-adherence
- Adolescence
- Psychologic disorder (depression)
- Cognitive impairment
- Substance abuse
- Negative beliefs in medication
Patient-Driven IS Minimization: Non-Adherence

High Symptom Distress
Development of NODAT
Increased time post transplant
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Medication costs
Poor access to medication
Poor aftercare planning
Poor physician-patient relationship
Poor physician communication

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Complex Medical Regimens
Higher Medication Toxicity
Lack of medication education
No pillbox/reminder system
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- Industry changes

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Causes of Kidney Allograft Failure
Antibody Mediated Rejection and Non-adherence
## Non-Adherence vs IF/TA

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<td>25%</td>
<td>13%</td>
</tr>
<tr>
<td>Poorly understood condition</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Multifactorial causes</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>No specific treatment</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Odds of Graft Failure</td>
<td>7 fold increase</td>
<td>4 fold increase</td>
</tr>
<tr>
<td>Recognized as a major challenge facing transplant</td>
<td>???</td>
<td>✓</td>
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Could something as obvious as adherence be the intervention that statistically improves long-term post transplant outcomes?

How can we quantify it?
Association of Non-Adherence at 1 yr and Outcomes
Impact of Non-Adherence on Outcomes

Synergistic effect of class II epitope mismatch with non-adherence

Tacrolimus Variability: Impact on Graft Failure

- BPAR, GL, BPCAN, doubling Scr

**Graft survival vs BPAR**
P=0.003

**Graft survival vs variability**
P=0.003
Tacrolimus Variability: Impact on Graft Failure

- Tacrolimus level variability calculated based upon trough levels at 6-12 months post transplant (MMF trough level variability was not correlated)
- Groups assigned based upon median of 14.9%
  - High variability: Mean variability 25.2%
  - Low variability: Mean variability 9.6%
- Variability did not predict 1yr BPAR

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<th>Control</th>
<th>Graft Failure</th>
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</thead>
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<tr>
<td>Low</td>
<td>52.5%</td>
<td>29.4%</td>
</tr>
<tr>
<td>High</td>
<td>47.5%</td>
<td>70.6%</td>
</tr>
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<th>Covariant</th>
<th>Univariate p value (HR)</th>
<th>Multivariate p value (HR)</th>
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<tr>
<td>Tac variability</td>
<td>0.001 (4.237)</td>
<td>0.003 (3.125)</td>
</tr>
<tr>
<td>BPAR 1yr</td>
<td>0.006 (3.567)</td>
<td>0.003 (3.390)</td>
</tr>
<tr>
<td>Recipient Age (adults)</td>
<td>0.018 (1.030)</td>
<td>0.005 (1.031)</td>
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Tacrolimus Variability: Impact on Late Outcomes

**Composite endpoint**
Late acute rejection (>1yr), or TG and total GL

**Composite endpoint**
Late acute rejection (>1yr), or TG and total GL (excluding death with function)

- Tacrolimus variability assessed only during stable doses >1year post txp
- Tac SD thresholds tested included breaks at 1.5, 2, 2.5, and 3. HR ↑ 27% for a each 1 unit Tac SD, respectively
- No significant changes when adjusted for age, sex, eGFR or AR at 1 year
Tacrolimus Variability as a Clinical Endpoint

• Tacrolimus variability is a predictor of poor outcomes regardless the cause
  – Nonadherence, drug interactions, etc

• Can tacrolimus variability be reliably quantitated?
  – Two extensive analysis methods recently reported

• Tacrolimus variability as a CLINICAL ENDPOINT
  – SURROGATE ENDPOINT
    • is expected to predict clinical benefit based upon epidemiologic, therapeutic, pathophysiologic or other scientific evidence
  – BIOLOGIC MARKER (biomarker)
    • A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention
Strategies to Impact Non-Adherence

• Simplify dosing regimens
  – Decrease frequency of administration
    • Once daily regimen – TAC, AZA, Pred with inferior efficacy
    • Once daily tacrolimus – Astagraf® and Envarsus®
      – Lower variability of tacrolimus after conversion from Prograf to Astagraf
        » Wu et al, Transplantation 2011; 92: 648-652
      – Improved adherence to tacrolimus once daily formulation: RCT using electronic monitoring
      – Economic Implications of Non-adherence and AMR with once daily TAC
        » Muduma et al, Journal of Medical Economics, 2015, 1-10

• Observed administration
  – Belatacept monthly infusions

• Develop novel agents with adherence component
Strategies to Impact Non-Adherence

- Electronic Medication Monitors (MEMS) predict patterns of early medication adherence
  - Tested with MMF, sirolimus and azathioprine in 195 kidney transplant recipients
  - Adherence between month 1-2 predicted adherence for 6mo (73%) and 12mo (92%)
  - Non-adherent patients more frequent, earlier AR and death censored graft loss
  - During month 1-3 – Adherence QID 84%, BID 91%, and QD 94%
Strategies to Impact Non-Adherence

- Ingestible Sensor for Measuring Medication Adherence
  - Tested in with ECMPS in kidney transplants with a 99.3% detection rate
  - Proteus Digital Health Feedback System-first FDA approved device, June 2015

Goals for Clinicians

• Implement formalized adherence programs
• Combined novel monitoring systems with patient specific interventions to improve adherence
Goals for Industry and FDA

• Expand utilization of FDA guidance in transplant registration trials
• Explore toxicity as a clinical endpoint
• Explore tacrolimus variability as a surrogate endpoint or biomarker
• Consider patient enrichment strategies based upon non-adherence risk factors
• Explore single Phase 3 study for approval
• Reward development of adherence-enhancing strategies
Conclusion

• Non-adherence is underestimated
• Improvements in adherence would impact ALL causes of graft loss
• Consider adherence enhancing strategies throughout transplant pharmaceutical development phases

*Prendergast and Gaston CJSAN 2010 Jul 5 (7) 1305-1311.