Literature Review 2010-Transplantation

Alexander Wiseman, M.D.
Associate Professor, Division of Renal Diseases and Hypertension
Medical Director, Kidney and Pancreas Transplant Programs
University of Colorado Health Sciences Center
Transplantation Top 10 in 2010

I. Outcomes of Kidney Transplantation: Reason for Optimism?

- GFR rate slopes have significantly improved among renal transplants in the US (Srinivas TR et al, Transplantation 2010)
- The Histology of Solitary Allografts at 1 and 5 Years after Transplantation (Stegall MD et al, Am J Transplant 2010)

II. Optimizing and Predicting Graft Survival

- MMF-based immunosuppression with sirolimus in renal transplantation: a randomized controlled Spare the Nephron trial (Weir MR et al, Kidney Int 2010)
- A phase II study of belatacept-based immunosuppression regimens vs CsA in renal transplant recipients (Vincenti F et al, Am J Transplant 2010)
- A simple tool to predict outcomes after kidney transplant (Kasiske BL et al, AJKD 2010)
- Inflammation in Areas of Tubular Atrophy in Kidney Allograft Biopsies: A Potent Predictor of Allograft Failure (Mannon R et al, Am J Transplant 2010)

III. Access to Transplant

- Outcomes of kidney transplantation in HIV-infected recipients (Stock PG et al, NEJM 2010)
- Access to kidney transplantation among the elderly in the US: a glass half full, not half empty (Schaeffner ES et al, CJASN 2010)
- Transplant nephrectomy improves survival following a failed renal allograft (Ayus JC et al, JASN 2010)
I. Outcomes of Kidney Transplantation: Reason for Optimism?

• Long-term renal allograft survival in the United States: a critical reappraisal (Lamb KE et al, Am J Transplant)

• GFR rate slopes have significantly improved among renal transplants in the US (Srinivas TR et al, Transplantation 2010)

• The Histology of Solitary Allografts at 1 and 5 Years after Transplantation (Stegall MD et al, Am J Transplant 2010)
Long-term renal allograft survival in the United States: a critical reappraisal

- Database analysis of graft survival from 1989-2005
- Slow improvement in graft t₁/₂ over time

<table>
<thead>
<tr>
<th>Transplant Subgroup</th>
<th>Actual Graft half-life, 1997 transplants</th>
<th>Projected Graft half-life, 2004 transplants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Recipients</td>
<td>Black Recipients</td>
</tr>
<tr>
<td>All Deceased donor transplants</td>
<td>8.2 y</td>
<td>6.3 y</td>
</tr>
<tr>
<td>SCD</td>
<td>8.9 y</td>
<td>6.8 y</td>
</tr>
<tr>
<td>ECD (1st tx)</td>
<td>5.1 y</td>
<td>4.4 y</td>
</tr>
<tr>
<td>Living Donor</td>
<td>12.0 y</td>
<td>8.7 y</td>
</tr>
</tbody>
</table>
Long-term renal allograft survival has improved due to improvements in early (not late) graft outcomes.

- Slopes of survival curves all parallel after first year
- Graft “Attrition rates” (% graft loss during a given era) only improved for the era in the first year post-transplant
- This suggests that we are better at preventing early graft loss, but have not made any improvements in preventing chronic graft loss

GFR slopes have significantly improved among renal transplants in the United States

- Database (SRTR) analysis of all adult kidney transplants from 2003-8
- GFR slopes from from 6-24 mo calculated
  - (those with graft loss were given a GFR value of 10 ml/min)

△GFR from 6-24 mo, by Year

<table>
<thead>
<tr>
<th>Year of Transplant</th>
<th>△GFR (ml/min) 6-24 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>-4.29</td>
</tr>
<tr>
<td>2004</td>
<td>-3.51</td>
</tr>
<tr>
<td>2005</td>
<td>-3.10</td>
</tr>
<tr>
<td>2006</td>
<td>-1.56</td>
</tr>
<tr>
<td>2007</td>
<td>-1.39</td>
</tr>
</tbody>
</table>

Rate of △GFR has improved significantly from 2003 to 2007!
GFR slopes have significantly improved irrespective of immunosuppressive regimen

- TAC/MMF-based regimens (at the time of transplant hospital discharge) were associated with only a slightly slower rate of GFR decline from 6-24 months

<table>
<thead>
<tr>
<th>Baseline Immunosuppression</th>
<th>GFR at 6 mo (ml/min)</th>
<th>ΔGFR (ml/min) 6-24 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAC/MMF/P (43%)</td>
<td>57.3</td>
<td>-2.7*</td>
</tr>
<tr>
<td>TAC/MMF (15%)</td>
<td>56.7</td>
<td>-2.3*</td>
</tr>
<tr>
<td>CSA/MMF/P (11%)</td>
<td>54.1</td>
<td>-2.5</td>
</tr>
<tr>
<td>CSA/MMF (1%)</td>
<td>53.0</td>
<td>-3.7</td>
</tr>
<tr>
<td>SRL/MMF/P (2%)</td>
<td>55.6</td>
<td>-3.2</td>
</tr>
<tr>
<td>Other (28%)</td>
<td>54.9</td>
<td>-3.2*</td>
</tr>
</tbody>
</table>

Progressive “CAN” (fibrosis) and calcineurin inhibitor nephrotoxicity as a cause of chronic graft loss?

961 biopsy samples from 120 SPK recipients over 10y:

At 5 years: CAN II/III in 66%, CNI nephrotoxicity in >50%
The Histology of Solitary Renal Allografts at 1 and 5 Years After Transplantation
Stegall MD et al, Am J Transplant. 2010 Nov 9

- Of 853 patients transplanted and receiving standard immunosuppression, 343 had 5y biopsy and 296 had paired 1 and 5y biopsy:

![Diagram showing distribution and outcomes of kidney transplants and biopsies.]

Those without 1/5y biopsy:
Mean GFR 50.4 ml/min

Those with 1/5y biopsy:
Mean GFR 51 ml/min
The Histology of Solitary Renal Allografts at 1 and 5 Years After Transplantation

- At 1y, 26% had **mild fibrosis**:
- At 5y:
  - 39% decreased to “none”
  - 38% “maintained mild”
  - 23% “increased to mod-severe”

- At 1y, 9% had **mod/severe fibrosis**:
- At 5y:
  - 20% decreased to “none”
  - 42% decreased to “mild”
  - 38% maintained “mod-severe”

Stegall MD et al, Am J Transplant. 2010 Nov 9
## Comparison of Histologic Findings in 2 Pivotal Studies at 1 and 5 Years After Transplantation

<table>
<thead>
<tr>
<th>Nankivell, NEJM 2003</th>
<th>Stegall, AJT 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1y “CAN”:</strong></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>94%</td>
</tr>
<tr>
<td>Stage II/III</td>
<td>25%</td>
</tr>
<tr>
<td><strong>5y “CAN”</strong></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>100%</td>
</tr>
<tr>
<td>Stage II/III</td>
<td>66%</td>
</tr>
<tr>
<td><strong>1y “Fibrosis”:</strong></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>39%</td>
</tr>
<tr>
<td>Stage II/III</td>
<td>15%</td>
</tr>
<tr>
<td><strong>5y “Fibrosis”</strong></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>44%</td>
</tr>
<tr>
<td>Stage II/III</td>
<td>19%</td>
</tr>
</tbody>
</table>

Much improved histology at 1 and 5 years, not universally progressive!
(due to TAC/MMF vs CsA/AZA, lower CNI levels, different pt populations?)
Quick summary - Reason for Optimism

- Graft survival rates have improved over time
- This improvement is primarily due to improvements in early (<1y) outcomes
- Rate of decline in GFR over the first 2y has significantly improved over the last 5 years
  - not due to a specific immunosuppression regimen
- Less fibrosis on protocol biopsies at 1 and 5 years than previous reports
II. Optimizing and Predicting Graft Survival

- MMF-based immunosuppression with sirolimus in renal transplantation: a randomized controlled Spare the Nephron trial (Weir MR et al, Kidney Int 2010)


- A simple tool to predict outcomes after kidney transplant (Kasiske BL et al, AJKD 2010)

- Inflammation in Areas of Tubular Atrophy in Kidney Allograft Biopsies: A Potent Predictor of Allograft Failure (Mannon R et al, Am J Transplant 2010)
“MMF-based immunosuppression with sirolimus in renal transplantation: a randomized, controlled Spare-the-Nephron trial”
Weir MR et al, Kidney Int. 2010 Dec 29

• **Purpose**
  – To evaluate efficacy and safety of maintenance immunosuppressive regimen of MMF+Sirolimus compared with that of MMF+CNI in renal allograft recipients

• **Methods**
  – Open label, prospective, randomized, multi-center study

---

**Randomization**

- **Patients 30-180 Days Post-Transplant**
  - Maintained on CNI+MMF ± Steroids

- **CNI+MMF**
  - MMF 1-1.5 g BID

- **Sirolimus+ MMF**
  - MMF 1-1.5 g BID
  - SRL Loading Dose: 2-10 mg
  - SRL trough: 5-10 ng/mL

**n=305**
The Spare-the-Nephron trial
12 and 24 month data

<table>
<thead>
<tr>
<th></th>
<th>MMF/Sirolimus</th>
<th>MMF/CNI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=148</td>
<td>n=151</td>
</tr>
<tr>
<td>%Change in eGFR at 12 months</td>
<td>+23.2%</td>
<td>+4.0%</td>
</tr>
<tr>
<td>%Change in eGFR at 24 months</td>
<td>+9.8%</td>
<td>+2.1%</td>
</tr>
<tr>
<td>Biopsy Proven Acute Rejection, %</td>
<td>9.5</td>
<td>11.3</td>
</tr>
<tr>
<td>Graft Loss, %</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Death, %</td>
<td>0</td>
<td>3*</td>
</tr>
<tr>
<td>Proportion of Patients DC Treatment for AEs,%</td>
<td>21</td>
<td>13</td>
</tr>
</tbody>
</table>

- Conversion from CNI to SRL was safe, well tolerated in ~80% of recipients, and resulted in a non-significant improvement in GFR at 2 yrs
- By itself, perhaps not compelling data to overcome “hassle factor” of transition, but suggests a reasonable strategy for immunosuppression especially if CNI-related side effect early post-transplant

Weir MR et al, Kidney Int. 2010 Dec 29
Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT)

Belatacept: new agent (costimulation blocker) given IV every 4 weeks

- 666 renal transplant recipients

- Basiliximab/MMF/Pred +:
  - “Less intensive” Belatacept
  - “More intensive” Belatacept
  - CsA

BENEFIT Results:

Acute rejection higher with Belatacept than CsA

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Cyclosporine</th>
<th>Belatacept LI</th>
<th>Belatacept MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>0</td>
<td>22%</td>
<td>22%</td>
</tr>
<tr>
<td>35</td>
<td>0</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>45</td>
<td>0</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Acute Rejection (%)
GFR and IF/TA better with Belatacept at 1 year (even those with acute rejection!)

<table>
<thead>
<tr>
<th>At 12 months:</th>
<th>MI</th>
<th>LI</th>
<th>CsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAN (IF/TA) @1 year</td>
<td>18%</td>
<td>24%</td>
<td>32%^</td>
</tr>
<tr>
<td>Calculated GFR (ml/min)</td>
<td>68</td>
<td>68</td>
<td>54*</td>
</tr>
</tbody>
</table>

Belatacept and PTLD
(pooled from 3 registration trials, reported in FDA Advisory Committee Briefing Document)

<table>
<thead>
<tr>
<th></th>
<th>Belatacept MI (n = 477)</th>
<th>Belatacept LI (n = 472)</th>
<th>CsA (n = 476)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTLD cases</td>
<td>8 (1.7%)</td>
<td>6 (1.3%)</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td>Site of presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>CNS</td>
<td>6</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>EBV recipient status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Positive</td>
<td>2*</td>
<td>4</td>
<td>0*</td>
</tr>
</tbody>
</table>

For EBV(-) recipients: 4-6x higher PTLD risk than CMS/UNOS registry
A simple tool to predict outcomes after kidney transplant


- Using USRDS/OPTN, and CMS data for patients who underwent deceased donor kidney transplant in 2000-2006 the authors used Cox proportional hazards analyses to develop separate tools for assessment:
  - (1) pretransplant,
  - (2) at 7 days posttransplant
  - (3) at 1 year posttransplant

- to predict subsequent risk of graft loss within 5 years of transplant
A simple tool to predict outcomes after kidney transplant

- **Pretransplant characteristics**- 11 variables (by order of contribution): donor age, recipient race, first vs subsequent transplant, years on dialysis, recipient age, primary cause of CKD, hepatitis C virus antibody status, donor history of HTN, recipient primary insurance coverage, donor cause of death, and HLA mismatches

- **At time of hospital discharge**- 8 variables were needed (by order of contribution): eGFR at hospital discharge (+/- DGF), donor age, primary cause of CKD, recipient race, recipient age, and years on renal replacement therapy (by first vs subsequent transplant)

- **At 12 months**- 6 variables were needed (by order of contribution): eGFR at 1 year posttransplant, recipient race, hospitalization during year 1 posttransplant, primary cause of CKD, recipient age, and recipient primary insurance coverage
A simple tool to predict outcomes after kidney transplant

• A clinician can estimate the risk pretransplant, at the
time of hospital discharge, and at 1 year posttransplant
by entering the information into a web-based calculator
to determine risk (www.txscores.org)
  – Variables that were not primary contributors to the “graft loss calculator”: PRA, acute rejection

• Authors’ conclusion: “it may help clinicians make
important decisions regarding selection of deceased
donor kidneys and posttransplant management
strategies.”
A simple tool to predict outcomes after kidney transplant

- Recipient: 64 yo white man with T2DM, on hemodialysis for 2.5 years, Medicare primary insurance, no prior transplants

- Donor: 57 yo, HTN, CVA, 2Ag match (ECD)

- Same recipient

- Same donor except 48 yo (not ECD)

49% probability of graft loss within 5 years

44% probability of graft loss within 5 years
Why are kidney allografts still failing?

• 7-center consortium, “Study of Long-Term Deterioration of Kidney Allograft Function (DeKAF)”

• Retrospective analysis of kidney biopsy data from 337 recipients

• Inclusion Criteria
  – a kidney or SPK transplant before 10-01-2005
  – underwent a clinically indicated kidney biopsy due to new onset deterioration of function, (increase in serum Cr but still ≤2 mg/dl) OR new onset proteinuria (prot/cr ratio ≥0.4)

ClinicalTrials.gov identifier: NCT00270712
Not all IF/TA is created equal?

- DeKAF study of biopsies in 337 patients with “new onset late graft dysfunction”:
  - Inflammation in areas of tubular atrophy (“iatr”) was associated with decreased graft survival
    - Was the most significant marker of graft failure, even after adjustments for C4d staining or donor specific antibody
  - Does this reflect ongoing alloimmune response?

Mannon R et al, Am J Transplant 2010; 10: 2066
Quick Summary-
Optimizing and Predicting Graft Survival

- Strategies to eliminate calcineurin inhibitors (tacrolimus, cyclosporine) remain attractive, with 1-2 year data showing better GFR
  - Need to see if this is sustained, and balance these strategies against side effects/tolerability and IV route paradigm

- Most graft outcomes are due to the recipient risk factors and greater education regarding ECD transplantation is needed

- Attention to inflammation in fibrosis (and potential treatment when identified) will be of significant interest in the future
III. Access to Transplant

• Outcomes of kidney transplantation in HIV-infected recipients (Stock PG et al, NEJM)

• Access to kidney transplantation among the elderly in the US: a glass half full, not half empty (Schaeffner ES et al, CJASN)

• Transplant nephrectomy improves survival following a failed renal allograft (Ayus JC et al, JASN)
Outcomes of Kidney Transplantation in HIV-Infected Recipients

- 150 HIV+ patients receiving transplants in a multicenter trial, 19 participating centers

- Inclusion criteria: CD4 T cell count > 200 with negative HIV RNA, on HAART therapy

- Cause of renal failure was HTN in 25% and HVAN in 24%

- 32% treated with thymoglobulin induction, 66% with tacrolimus.
Outcomes of Kidney Transplantation in HIV+ Recipients

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Pt Survival</th>
<th>Graft Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1y</td>
<td>3y</td>
</tr>
<tr>
<td>HIV+</td>
<td>94.6</td>
<td>88.2</td>
</tr>
<tr>
<td>Registry comparison:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age&gt;65</td>
<td>91.8</td>
<td>79.5</td>
</tr>
<tr>
<td>Overall</td>
<td>96.2</td>
<td>90.6</td>
</tr>
</tbody>
</table>

Acute rejection significantly higher, no difference in infectious complications in HIV+ recipients

Acute Kidney-Allograft Rejection:

1y: 31%
3y: 41%

Changes in CD4+ T-Cell Count Post-transplant, According to Thymoglobulin Induction Status:

Depleting Ab lowered CD4 count with long term effects, but did not impact risk of opportunistic infection

Access to kidney transplantation among the elderly in the United States: a glass half full, not half empty

- Using USRDS data for all transplants 1995-2006, the authors examined likelihood of transplant, by organ type
Elderly patients much more likely to receive transplants in 2007 vs 1995, due to ECD/LD utilization

Likelihood of transplantation in 2006 vs 1995

Hazard Ratio

Age

60-64  65-69  70-74

Likelihood of SCD, ECD, and LD Tx

Year of ESRD

Schäffner E S et al. CJASN 2010;5:2109
Transplant nephrectomy improves survival following a failed renal allograft
Ayus JC et al, JASN 2010;21(2):374-80

- Problem: A failed allograft may act as a source of chronic inflammation when initiating dialysis, leading to anemia, hypoalbuminemia, elevated CRP, with no controlled data supporting immunosuppression taper or nephrectomy after graft failure

- Study: USRDS cohort of 10,951 patients who returned to maintenance dialysis after a failed kidney transplant (function for >90d) between 1994 and 2004
- 3451 of the cohort underwent nephrectomy following graft loss during the study period (mortality within 30d of NTX was 1.5%)
- 901 of the entire cohort of patients received subsequent transplant
Transplant nephrectomy (after return to dialysis) was associated with lower mortality and a higher re-transplant rate.

- Should not withhold transplant nephrectomy due to perceived mortality risk or risk of increased sensitization/decrease in potential for re-transplant.

![Graph showing mortality rates and rate of repeat kidney transplantation](image)

- Mortality rate/100 person yr:
  - Tx NTX: 32.0
  - No Tx NTX: 36.0
  - P = 0.0024

- Rate of Repeat Kidney Transplantation:
  - Tx NTX: 10.0%
  - No Tx NTX: 4.1%
  - P < 0.001

(The Last) Quick Summary- Access to Transplant

• HIV:
  – In carefully selected patients, patient- and graft-survival rates were high at 1 and 3 years, with no increases in complications associated with HIV infection.
  – High rejection rates surprising and indicate the need for better immunotherapy

• Elderly:
  – A higher rate of transplant (especially for 70-74 yo) over the last decade demonstrates excellent access to transplant

• Prior Failed Transplant:
  – Still no trials guiding us regarding immunosuppression taper, but if transplant nephrectomy is indicated, should be pursued