Literature Review: Transplantation
July 2010-June 2011

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Assistant Professor, Kidney and Pancreas Transplant Program, Renal Division, UC Denver

• Kidney Donation
  – Accepting Kidneys from Older Living Donors: Impact on transplant Recipient Outcomes (Young et al, AJT: April 2011)
  – Living Donor Age and Transplant Outcomes (Noppakun et al, AJT: June 2011)

• Induction
  – Alemtuzumab Induction in Renal Transplantation (Hanaway et al, NEJM: May 2011)

• Graft Outcomes
  – GFR rate slopes have significantly improved among renal transplants in the US (Srinivas et al, Transplantation: December 2010)
  – The Histology of Solitary Allografts at 1 and 5 Years after Transplantation (Stegall et al, AJT: April 2011)
  – Outcomes of kidney transplantation in HIV-infected recipients (Stock et al, NEJM: November 2010)

• CNI Minimization
  – Everolimus-based, CNI-free regimen in recipients of de-novo kidney transplants: an open-label, randomised, controlled trial (Budde et al, Lancet, March 2011)
  – MMF-based immunosuppression with sirolimus in renal transplantation: a randomized controlled Spare the Nephron trial (Weir et al, Kidney Int: April 2011)
  – Belatacept-based regimens versus a cyclosporine A-based regimen in kidney transplant recipients: 2-year results from the BENEFIT and BENEFIT-EXT studies (Larsen et al, Transplantation December 2010)
Accepting kidneys from older living donors: impact on transplant recipient outcomes
Young et al, AJT 2011; 11: 1–8

- **Objective**: Compare outcomes of death and/or graft loss in recipients of older living donor kidneys (>60yo) to recipients of younger living and deceased standard criteria kidneys.

- **Methods**: Retrospective cohort study using electronic healthcare data from the “Trillium gift of Life Network”: Ontario’s central organ and tissue donation agency.

<table>
<thead>
<tr>
<th></th>
<th>Living Donor Recips</th>
<th>Deceased donor recips</th>
<th>Living Kidney Donors</th>
<th>Deceased donors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥60yo (n=73)</td>
<td>&lt;60yo (n=1187)</td>
<td>(&lt;60yo) (n=1400)</td>
<td></td>
</tr>
<tr>
<td>Age (mean)</td>
<td>49</td>
<td>45*</td>
<td>50</td>
<td>63</td>
</tr>
<tr>
<td>Gender (♀) %</td>
<td>33</td>
<td>40</td>
<td>37</td>
<td>49</td>
</tr>
<tr>
<td>HD duration</td>
<td>23</td>
<td>23</td>
<td>49*</td>
<td></td>
</tr>
<tr>
<td>MDRD GFR</td>
<td></td>
<td></td>
<td></td>
<td>84</td>
</tr>
</tbody>
</table>

*Significantly different from younger group.
Acceptable graft outcomes in recipients of older living donor kidneys (median follow-up of 4 yrs)

Grafts from younger vs. older donor

<table>
<thead>
<tr>
<th>Recipient Outcome (MV adjusted HR*)</th>
<th>Younger (&lt;60yo) donor</th>
<th>Older (≥ 60yo) donor</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total graft loss</td>
<td>1.0 (reference)</td>
<td>1.56 (.98-2.49)</td>
<td>.06</td>
</tr>
<tr>
<td>Death</td>
<td>1.0 (reference)</td>
<td>2.73 (1.39-5.35)</td>
<td>.004</td>
</tr>
<tr>
<td>Death-censored graft loss</td>
<td>1.0 (reference)</td>
<td>.84 (.34-2.11)</td>
<td>.72</td>
</tr>
</tbody>
</table>

Grafts from standard criteria deceased vs. older donor

<table>
<thead>
<tr>
<th>Recipient Outcome (MV adjusted HR*)</th>
<th>Deceased (&lt;60yo) donor</th>
<th>Older (≥ 60yo) donor</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total graft loss</td>
<td>1.0 (reference)</td>
<td>1.29 (.8-2.08)</td>
<td>.3</td>
</tr>
<tr>
<td>Death</td>
<td>1.0 (reference)</td>
<td>1.83 (.96-3.48)</td>
<td>.07</td>
</tr>
<tr>
<td>Death-censored graft loss</td>
<td>1.0 (reference)</td>
<td>.74 (.34-1.62)</td>
<td>.45</td>
</tr>
</tbody>
</table>

* Adjusted for recipient age, HD duration, donor GFR, year of transplant

- Authors suggest increased death rate in older donor recipients due to residual confounding related to health factors not accounted for (opposed to the older graft itself)
- Study suggests kidneys from donors >60yo can be expected to function at least as well as those from younger or deceased donors, as long as you stay alive.
Living donor age and kidney transplant outcomes
Noppakun et al, AJT 2011; 11: 1279–1286

• So, should all recipients accept kidneys from an older donor?
  – Eg, 18 yo recipient and 62 year old potential donor?

• Mayo group assessed the relationship between living donor and recipient age
  – All adult recipients (>18) of living donor kidneys at their center from 1980-2007
  – 3 cohorts:
    1. Donor age < recip (5yrs): n=477.
    2. Donor age = recip (within 5 yrs): n=379.
    3. Donor age > recip: n=207.

• Suggests graft quality is important predictor of graft survival in younger recipients, whereas patient survival is most important predictor in older recipients.
Induction with alemtuzumab and steroid-free regimens both looking for a place in kidney transplant protocols

- Induction therapy has been increasingly used over the past decade, contributing in part to reductions in early rejection and graft loss.
- Alemtuzumab (Campath) is a monoclonal anti-CD52 (expressed on lymphocytes) antibody. Use in the US has been slow to catch on:
  - Profound and prolonged lymphocyte depletion
  - Increased rates of infection
  - Increased rates of Ab-mediated rejection and late rejection
- Early steroid withdrawal protocols are tempting due to reduced potential for CV and bone disease.
  - Most studies have shown modest reductions in CV risk factors (wt gain, hyperlipidemia) at the expense of increased acute rejection.

>80% of kidney transplant recipients receive induction.
Alemtuzumab induction in renal transplantation
Hanaway et al, NEJM 2011;364:1909-19

- Prospective, open-label, randomized, multicenter controlled trial comparing alemtuzumab induction to “conventional therapy” ( basiliximab for low immunologic risk, r-ATG for high immunologic risk) in an early (5 day) steroid withdrawal protocol.
- Funded by Astellas, all patients received tacrolimus (trough 7-14 x 90 days, then 4-12ng/ml), cellcept or Myfortic (2g or 1440mg/day), steroid taper at day 5.

1º endpoint: Biopsy-proven Acute rejection (BPAR) at 12 and 24 mo
Campath associated with less AR, but the AR occurs late

<table>
<thead>
<tr>
<th>Month</th>
<th>Campath</th>
<th>Conventional</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>3</td>
<td>15</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
<td>17</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>36</td>
<td>13</td>
<td>20</td>
<td>.03</td>
</tr>
</tbody>
</table>

- Graft survival similar in all groups.
- Higher overall cancer rate in campath treated patients
  - Vs. basiliximab: more leukopenia, more serious infections
  - Vs. r-ATG: similar side effect profile
- Study suggests acceptable AR rates in steroid withdrawal protocols with campath or r-ATG, more immune protection vs. IL2-RA at expense of side effects. Campath = more late AR (late AR = bad!).
Graft outcomes at a glance

1. **Long-term renal allograft survival in the United States: a critical reappraisal** (Lamb et al, AJT: March 2011)

2. **GFR rate slopes have significantly improved among renal transplants in the US** (Srinivas et al, Transplantation: December 2010)

3. **The Histology of Solitary Allografts at 1 and 5 Years after Transplantation** (Stegall et al, AJT: April 2011)

4. **Outcomes of kidney transplantation in HIV-infected recipients** (Stock et al, NEJM: November 2010)
Lack of improvement in long-term graft outcomes: 2004

Despite considerable improvements in AR rates, long term graft outcomes remained relatively unchanged over the same time period.

Long-term renal allograft survival in the United States: a critical reappraisal

- Database analysis of graft survival from 1989-2005
- Slow improvement in graft $t_{1/2}$ over time

**Graft $t_{1/2}$**

<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)

\[\Delta GFR \text{ from } 6-24 \text{ mo, by Year}\]

<table>
<thead>
<tr>
<th>Year of Transplant</th>
<th>(\Delta GFR \text{ (ml/min)})</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 \(\Delta GFR\) 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 of kidney transplantation outcomes]

  - 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></th>
<th>Nankivell, NEJM 2003</th>
<th>Stegall, AJT 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1y “CAN:”</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>94%</td>
<td>Stage I</td>
</tr>
<tr>
<td>Stage II/III</td>
<td>25%</td>
<td>Stage II/III</td>
</tr>
<tr>
<td><strong>5y “CAN”</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>100%</td>
<td>Stage I</td>
</tr>
<tr>
<td>Stage II/III</td>
<td>66%</td>
<td>Stage II/III</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?)
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

Pt Survival

<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
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
CNI minimization at a glance

1. Everolimus-based, CNI-free regimen in recipients of de-novo kidney transplants: an open-label, randomised, controlled trial (Budde et al, Lancet, March 2011)

2. MMF-based immunosuppression with sirolimus in renal transplantation: a randomized controlled Spare the Nephron trial (Weir et al, Kidney Int: April 2011)

3. Belatacept-based regimens versus a cyclosporine A-based regimen in kidney transplant recipients: 2-year results from the BENEFIT and BENEFIT-EXT studies (Larsen et al, Transplantation December 2010)
mTOR-Ips: still searching for a place in kidney transplant

- Many trials have attempted to reduce CNI exposure by using several mTOR-I-based strategies:
  - Avoidance: No exposure to CNI at all
    - ELITE-Symphony study: de novo sirolimus/MMF/prednisone regimen with more AR, worse graft survival vs. CNI-based regimens
  - Withdrawal: CNI is withdrawn from an mTOR-I based regimen
    - RMR study: sirolimus-treated CNI-withdrawn patients with improved GFR but more AR at 3 years
  - Conversion: CNI-based regimen converted to mTOR-I based at some point post-transplant
    - CONVERT study: CNI/MMF/prednisone converted to SRL/MMF/prednisone at 6mo to 10yrs post transplant. Poor outcomes in those with GFR<40cc/min, proteinuria.
“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
The Spare-the-Nephron trial
12 and 24 month data

- 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

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Weir MR et al, Kidney Int. 2010 Dec 29
Everolimus-based, CNI-free regimen in recipients of de-novo kidney transplants: an open-label, randomised, controlled trial (ZEUS trial)


- **Everolimus (EVL)** is a structural analog of sirolimus with shorter half life and improved bioavailability
  - Approved by FDA April 2010 for use in kidney recipients in combination with low dose CsA, steroids, and basiliximab induction

- **Purpose**: Evaluate efficacy and safety of CNI -> EVL conversion at 4-5 months post-transplant, +MPA, prednisone, in stable patients (no proteinuria, no rejection, Scr <2.5mg/dl).

- **Methods**: Prospective, multicenter randomised controlled trial

503 enrolled at transplant
Basiliximab induction
CsA/MPA/steroid

CsA trough 150-220 ng/ml

300 randomized at month 4-5

CsA/MPA/steroid
N=146
CsA:120-180ng/ml (4-6)
100-150ng/ml (6-12)

EVL/MPA/steroid
N=154
EVL: 3-8ng/ml until CsA stopped, then 6-10
12 month data show improved GFR, more rejection with EVL

- eGFR (1st endpoint)
  - 12mo GFR in EVL patients with AR: 70cc/min
  - Despite overall similar AE rates, EVL associated with ↑ thrombocytopenia, anemia, diarrhea, hyperlipidemia, proteinuria

<table>
<thead>
<tr>
<th></th>
<th>CsA n=146</th>
<th>EVL n=154</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 month GFR</td>
<td>61.9</td>
<td>71.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BPAR entire study (%)</td>
<td>15</td>
<td>15</td>
<td>ns</td>
</tr>
<tr>
<td>BPAR from randomization (%)</td>
<td>3</td>
<td>10</td>
<td>.0362</td>
</tr>
<tr>
<td>Graft Loss</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Death, %</td>
<td>1</td>
<td>3*</td>
<td>ns</td>
</tr>
<tr>
<td>% of Patients DC Treatment</td>
<td>19</td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>

- Study suggests improved renal function with CNI -> EVL conversion at expense of increased late AR episodes, side effects. Widespread acceptance likely to be hindered by hassles of conversion in otherwise stable patients, logistics of intensified “late” rejection monitoring by centers
Belatacept-based regimens versus a cyclosporine A-based regimen in kidney transplant recipients: 2-year results from the BENEFIT and BENEFIT-EXT studies

Larsen et al, Transplantation 2010;90: 1528–1535