Current “Hot Topics” in Kidney Transplantation

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Outline

• Why do grafts fail, and why do they fail more often in the United States?

• Predictors of untoward events: rejection, opportunistic infection

• Novel Immunosuppression

• Tolerance???
Long-term renal allograft survival in the United States: a critical reappraisal
Lamb KE al, Am J Transplant 2011;11(3):450-6

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

Kidney Graft Survival in Europe and the United States: Strikingly Different Long-term Outcomes

Gondos et al, Transplantation 2012
Glomerular disease is the most common cause of graft loss

- Mayo Clinic: 1317 consecutive kidney transplants 1996-2006, 330 with graft loss at mean 50.3 mo f/u
  - 138 (43.4%) due to death
  - 39 (11.8%) due to 1° nonfunction
  - 153 (46.3%) due to graft failure:

  98% had biopsies (mean 4.7 mo prior to graft loss)

- Conclusion: glomerular pathology most common cause of graft loss other than death

Why do kidneys fail?

Mayo Clinic: 1317 consecutive kidney transplants 1996-2006, biopsies performed in patients with failing grafts at a mean 4.7 mo prior to graft loss

- **Of “IF/TA”**
  - 1/4 history of acute rejection

- **Of “glomerular disease”**
  - 40% “transplant glomerulopathy” (~HLA Ab?)

- ~1/3 of graft loss is linked to alloimmune/rejection response

Evolution and Clinical Pathologic Correlations of *De Novo* Donor-Specific HLA Antibody Post Kidney Transplant

- 315 consecutive KTX recipients followed for mean 6.2 years, protocol screening for DSA and protocol/clinical indication biopsies assessed

Graft survival strongly associated with \textit{de novo} DSA formation

Causes of late allograft failure

65% of subsequent failures could be attributed to ABMR, probable ABMR, or mixed; 48% were nonadherent.

J Sellares et al Am J Transplant 2012
Proposed model of the natural history of de novo DSA

Diagnosis of Acute Rejection—within and beyond the biopsy

• Additional features of the biopsy:
  – Genetic analysis
  – Cellular phenotyping (NK cells, macrophage/monocytes)
  – Non-HLA antibodies

• Urine/blood:
  – mRNA (perforin, granzyme B, FOXP3, TIM-3)

• Blood:
  – Cell function assays (IL-6 secretion, ELISPOT for IFN-γ; CD4 T cell ATP release)
  – Prospective monitoring for de novo anti-HLA Ab (DSA)
Urinary mRNA transcripts: Can they diagnose rejection?

- Comparison of urinary cell levels of mRNAs (rtPCR) in 21 recipients with graft dysfunction and BPAR, and 25 recipients with stable graft function and normal biopsy results.

- ROC curve analysis:
  - Acute rejection sensitivity 95% specificity 92% (AUC 0.98, P<0.0001) using a combination of levels of mRNA for OX40, OX40L, PD-1, and Foxp3.
  - Renal Transplant Monitoring (FOXP3, Granzyme B, Perforin, IP10) CPT Code(s): 83891, 83902, 83898, 83896
  - “This test was developed and its performance characteristics have been determined by Quest Diagnostics.”

Afaneh C et al, Transplantation 2010; 90: 1381
PBMC secretion of IL-6: Can this diagnose rejection?

- 64 patients with acute dysfunction underwent cytokine analysis at the time of biopsy.
- 21 cytokines from blood PBMCs measured.
- 29 with rejection, 35 without rejection on biopsy (other dx CAI, GN, ATN).
- Serum IL-6 found to be the best predictor of AR on biopsy.

- **ROC curve analysis:**
  - The measurement of IL-6 with a cutoff of 85 pg/ml “can exclude acute rejection with a sensitivity of 92%”.
  - “Easy, cheap, and fast”

De Serres SA et al, CJASN 2012; 7:1018
In the setting of delayed graft function (DGF): is it ATN or acute rejection?

- T-cell immunoglobulin domain, mucin domain (TiM-3) is selectively expressed on the surface of T-helper (Th)1 cells
- Tim-3 mRNA expression in biopsies, peripheral blood leukocytes (PBL) and urinary cells (UC) were studied in 160 biopsies from 115 patients:

Manfro RC et al, Transplantation 2008; 86: 1869
Can one distinguish BKV from rejection using urine chemokines?

- CXCL9 and CXCL10 are induced by IFNγ: can a urinary chemokine assay determine AR from BKV or other causes of graft dysfunction?
- 156 subjects categorized as: healthy volunteer, stable KTX, AR, BKV, with CNI toxicity, or IFTA)

 ROC curve for CXCL9: c-statistic 0.87 (sensitivity 86%, specificity 80%) for AR or BKV vs other causes)

- Difficult to segregate the inflammation of BKV vs the inflammation of AR!

Jackson JA et al, Am J Transplant 2011; 11: 2228
Conclusions/Future Directions

• Acute rejection remains an important cause of early morbidity and later graft dysfunction/loss

• Refinements in the diagnosis of rejection (beyond Banff) are key to developing better treatment alternatives

• Many questions remain:
  – Do we treat inflammation in areas of IFTA? If so, how?
  – Do we treat +DSA? If so, when and how?
  – How to treat the patient with “subacute” antibody-mediated rejection?
The Symphony Trial:  
Acute rejection, comparing immunosuppressive regimens

- 12-month randomized open-label multicenter trial of 1645 KTX
- 4 Treatment arms (IL2ra induction in “low” arms, MMF/Prednisone for all)
  - Standard: CSA 150-300 ng/ml x 3 months, then 100-200 ng/ml

At 12 months:

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Acute Rejection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSA “standard”</td>
<td>25.8</td>
</tr>
<tr>
<td>CSA (50-100 ng/ml)</td>
<td>24.0</td>
</tr>
<tr>
<td>TAC (3-7 ng/ml)</td>
<td>12.3*</td>
</tr>
<tr>
<td>SRL (4-8 ng/ml)</td>
<td>37.2</td>
</tr>
</tbody>
</table>

NEJM 2007; 357: 2562-75
New immunosuppressive agents: progress and pitfalls

Meds that have been withdrawn or no longer supported:

- OKT3, h-OKT3 (anti-CD3)
- Daclizumab (IL2ra)
- Efalizumab (anti-LFA1)
- Alefacept (anti-CD2)
- Sotrastaurin (PKC inhibitor)
- Diannexin (PGE2 inhibitor)

Meds in development/recent approval:

- Everolimus (USA in 2010)
- Belatacept (CTLA4-Ig, USA in 2011)
- Tofacitinib (JAK3 inhibitor)
- ISKP (Anti-CD40 mAb)
- TOL101 (anti-αβ TCR IgM)

Belatacept: Mechanism of Action

Binds to CD80/86 on APCs, preventing interaction with CD28 and costimulatory signal (signal 2) on T cells

- No cell division
- No cytokine production
- Anergy
- Apoptosis.
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

666 patients

226 pts low Belatacept (LI)
10 mg/kg IV Day 1, 5, 14, 28 q4 week x 3
From mo 3: 5 mg/kg IV q4 week

219 pts high Belatacept (MI)
10 mg/kg IV Day 1, 5, 14, 28 q2 week x 3 q4 week x 3
From mo 6: 5 mg/kg IV q4 week

221 pts CsA
100-400 ng/ml x 28d
From mo 1: 150-250 ng/ml

BENEFIT Results:
Acute rejection higher with Belatacept than CsA

- Belatacept MI: 22%
- Belatacept LI: 17%
- Cyclosporine: 7%
BENEFIT: 3-Yr Sustained Improved Renal Function With Belatacept vs Cyclosporine

Projected Mean Graft Half-life

Percentage of patients with a functioning graft

Years after transplant

Presented by Schnitzler et al, ATC, May 1, 2011
PTLD Risk Concentrated in EBV (-) Recipients (4-5x increased risk)

*Does not include 1 EBV unknown patient in the belatacept MI group, and 1 EBV unknown in the cyclosporine group. There are no cases of PTLD in CsA EBV(+) patients.*
Attempts at “Tolerance”
Ablative therapy and HCT reconstitution: The degree of chimerism may dictate success

Too Little (no chimerism?):
- Acute rejection
- Chronic rejection

Too much (full chimerism):
- GVHD
- Infections

“Just right”: microchimerism?
HLA-mismatched renal transplantation without maintenance immunosuppression

- 5 patients with ESRD age 22-46 with 1 haplotype mismatched living donors
- Combined kidney transplant with donor bone marrow infusion

Pre-transplant:
- Days -5, -4: Cyclophosphamide 60 mg/kg/d x 2
- Day -1: Thymic irradiation 700 cGy + CsA 5 mg/kd IV

Peritransplant:
- Days -1, 0, 1: Anti-CD2 monoclonal Ab

Post-transplant:
- CsA 8-12 mg/kg/d target trough 250-350 ng/ml, goal to discontinue

*(After patient #3: Rituximab 375 mg/m² on days -7 and -2 and Prednisone 2mg/kg d0-10 added)*

NEJM 2008; 358: 353
Clinical Characteristics and outcomes of the 5 subjects:

### Table 1. Patient Characteristics and Results of Laboratory Tests.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age</th>
<th>Original Disease</th>
<th>Pretransplantation PRA</th>
<th>Chimerism†</th>
<th>Discontinuation of Immunosuppressive Therapy</th>
<th>Kidney Survival</th>
<th>Current Serum Creatinine Level</th>
<th>Creatinine Clearance</th>
<th>Antidonor Alloantibody</th>
<th>Banff Score‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Day 7</td>
<td>Day 21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>22</td>
<td>Alport’s syndrome</td>
<td>45§</td>
<td>Undetectable</td>
<td>Day 240</td>
<td>&gt;1932</td>
<td>1.2</td>
<td>61</td>
<td>None</td>
<td>01000G0; clctctcv0c0g0</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>22</td>
<td>MPGN type 1</td>
<td>0</td>
<td>Undetectable</td>
<td>Day 422</td>
<td>&gt;1666</td>
<td>1.5</td>
<td>75</td>
<td>None</td>
<td>01000G0; clctctcv0c0g0</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>39</td>
<td>Polycystic kidney disease</td>
<td>52‡</td>
<td>Undetectable</td>
<td>Not discontinued</td>
<td>10</td>
<td>Underwent second kidney transplantation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>25</td>
<td>Alport’s syndrome</td>
<td>0</td>
<td>Undetectable</td>
<td>Day 244</td>
<td>&gt;1050</td>
<td>1.5</td>
<td>60</td>
<td>New antidonor HLA class II antibody</td>
<td>01000G0; clctctcv0c0g0</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>46</td>
<td>Polycystic kidney disease</td>
<td>0</td>
<td>T cell 15%, monocytes 19%, GRN 86.5%</td>
<td>Day 272</td>
<td>&gt;707</td>
<td>1.8</td>
<td>71</td>
<td>None</td>
<td>01000G0; clctctcv0c0g0</td>
</tr>
</tbody>
</table>

- All patients with transient chimerism
- 1 of 5 with irreversible humoral rejection
- 4 of 5 with immunosuppression withdrawal and function 2-5 years

NEJM 2008; 358: 353
Immunosuppression tapering in the 4 subjects with functioning grafts

- Immunosuppression removed by day 240-422

- 2 of 4 treated for humoral rejection
  - patient 2: day 45
  - patient 5: day 12

  - another with DSA formation (patient 4: day 304)
Northwestern Protocol

- 8 patients underwent conditioning with fludarabine, cytoxan, and total body irradiation prior to LD kidney transplant
- Donor “Facilitator cells” (dendritic cell lineage) with hematopoetic cells infused at day +1 following transplant
- Immunosuppression tapered over 6-12 months depending upon clinical function and presence of chimerism

Novel results: 100% durable chimerism

**PRO:** 5 of 8 patients demonstrated durable chimerism (cell lines were 100% donor origin) without GVHD or engraftment syndrome, no immunosuppression from 1 year post-transplant

**CON:** 1 pt with viral sepsis and hemorrhagic necrosis of KTX at month 3; 1 with recurrent membranous GN at 1 year (had lost chimerism at month 5)

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PMN count in month 1 post-transplant  % donor chimerism to 30 months

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