Recognition and Treatment of Chronic Allograft Dysfunction

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RECOGNITION: Terminology

• Chronic allograft dysfunction
• Chronic allograft nephropathy
• Interstitial fibrosis/tubular atrophy
• Chronic rejection
  – T cell mediated
  – Antibody mediated
• Calcineurin inhibitor nephrotoxicity
Chronic allograft nephropathy (CAN) is now segregated by immunological etiology vs IF/TA

Chronic allograft nephropathy:

“The histologic sequelae of a series of pathologic insults that result in incremental and cumulative damage to nephrons within the transplanted kidney”

- Chronic cellular or humoral rejection
- Calcineurin inhibitor nephrotoxicity
- Interstitial fibrosis and tubular atrophy (IF/TA)

- CAN: a clinical syndrome of renal function decline, proteinuria, and hypertension

2. Li C et al, Nat Rev Nephrol 2009; 5: 513
• Chronic Antibody-mediated rejection
  – Glomerular double contours, and/or
  – peritubular capillary basement membrane multilayering, and/or
  – interstitial fibrosis/tubular atrophy, and/or
  – fibrous intimal thickening in arteries,
    - C4d+

• Chronic T-cell-mediated rejection
  – Chronic allograft arteriopathy:
    – arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neo-intima
Calcineurin inhibitor nephrotoxicity

*De novo* arteriolar hyalinosis (excluding other etiologies) +/- striped fibrosis

961 biopsy samples from 120 SPK recipients over 10y:

CNI nephrotoxicity is detected in ~100% patients at 10 years post-transplant

Interstitial Fibrosis/Tubular Atrophy (IF/TA): ~40% of patients at 2 years with TAC/MMF

- 240 patients randomized:
  - Protocol biopsy at 1, 2, 3, and 6 months and treatment, vs
  - Biopsy at 6 months (control)
- 160 patients: Bx at 24 months
  - (74 in biopsy arm, 86 in control arm)
- All patients on TAC/MMF/Prednisone
  - (goal TAC 8±2 ng/ml from months 4-24)
- eGFR in both groups at 24 months was 74 ml/min

<table>
<thead>
<tr>
<th>IF/TA ≥ 2 (25-50% of core):</th>
<th>Protocol Biopsy arm</th>
<th>Control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implantation</td>
<td>3.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Month 6</td>
<td>34.8%</td>
<td>20.5%</td>
</tr>
<tr>
<td>Month 24</td>
<td>48.2%</td>
<td>38.5%</td>
</tr>
</tbody>
</table>

Rush DN et al, Transplantation 2009: 88: 897
Why do kidneys fail?

- 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:

- Conclusion: glomerular pathology most common cause of graft loss other than death, not CNI nephrotoxicity

Why do kidneys fail?

- Of “IF/TA”
  - 1/4 history of acute rejection
  - 1/4 history of BKV
  - 1/6 recurrent pyelo
  - ?Poor graft/CNI/Other…

- Of “glomerular disease”
  - 40% “transplant glomerulopathy” (~HLA Ab?)
  - 40% “recurrent” GN
  - 20% “de novo” GN

- ~1/3 of graft losses can be directly or indirectly related to alloimmune injury
- Unusual for grafts to fail with a “pure” diagnosis of CNI nephrotoxicity

Impact of Type of Acute Rejection on Graft Survival: AUST/NZ 1997-2004

- Vascular rejection portends worse outcomes than cellular rejection

McDonald S et al, Am J Transplant 2007; 7: 1201
Hazard ratio* for graft loss after 6 months from first acute rejection episode
AUST/NZ 1997-2004

<table>
<thead>
<tr>
<th>Response to therapy</th>
<th>All Acute Rejection</th>
<th>Cellular rejection alone</th>
<th>Vascular rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Good” (return to baseline)</td>
<td>1.61</td>
<td>1.25 (ns)</td>
<td>2.35</td>
</tr>
<tr>
<td>“Poor”</td>
<td>1.88</td>
<td>1.74</td>
<td>2.23</td>
</tr>
</tbody>
</table>

*Multivariate analysis, P<0.05 for all HR except (ns)

- Even with “good” response to therapy, vascular rejection was associated with a >2-fold increased risk of chronic graft loss
- “Good” response to therapy for cellular rejection posed no greater risk for graft loss

McDonald S et al, Am J Transplant 2007; 7: 1201
The presence of HLA antibodies post-transplant predicts 4-year graft survival

1239 pts screened: if + HLA Ab, ~5% worse graft survival per year

Deceased donor tx

Living donor tx

BK Virus Nephropathy

- Uncommon before 1995, now diagnosed in 2-10% of all kidney transplants

- Usually diagnosed 6 months-2 years after transplant

- Related to over-immunosuppression, reactivation of virus latent in transplanted kidney

- Usually leads to graft loss unless identified early

Viral inclusion bodies within tubular epithelial cells, with associated TI inflammation

Wiseman AC, AJKD 2009
Proposed histologic “patterns” of PVAN

• A: viral cytopathic changes with no or negligible inflammation or tubular atrophy

• B: viral cytopathic changes with significant interstitial inflammation and atrophy of renal tubules
  – b1: < 25% of the core
  – b2: 25-50% of the core
  – b3: >50% of the core

• C: rare viral cytopathic changes in atrophic tubules, in a background of extensive tubular atrophy/fibrosis and chronic inflammation (end-stage PVAN).

• Graft outcomes:
  • A: 13% graft loss
  • B1: 40% graft loss
  • B2: 56% graft loss
  • B3: 78% graft loss
  • C: 100% graft loss

Blood pressure at 12 months following transplant predicts graft survival

Opelz et al, JASN 2006; 17: 3257
Sustained proteinuria >0.5 g/d is associated with graft loss, death and CV events.

Of 532 patients, 36.4% had persistent proteinuria >0.5 g/d.

Among those without preexisting CV disease:
- 35.4% of patients with proteinuria had CV event.
- 14.6% of patients without proteinuria had CV event.

Transplantation. 2002;73:1345
Degree of proteinuria predicts graft outcome and underlying disease

- Of 613 patients, 45% had proteinuria at 1y
- Proteinuria was associated with graft loss in a graded fashion
- Proteinuria >1.5 g/d was associated with glomerular pathology (1y protocol bx)

Amer H et al, Am J Transplant 2007;7: 2748
Chronic Allograft Dysfunction: Management

**KNOWN:**
- Minimize acute rejection
- Avoid BKV
- Hypertension control
- Low threshold for biopsy

**UNKNOWN:**
- Protocol biopsy?
- Treat proteinuria?
- What to do with *de novo* anti-HLA Ab?
- Alter immunosuppression?
- What to do with IF/TA?
The Symphony Trial: Defining today’s “Gold Standard”

- 12-month randomized open-label multicenter trial of 1645 KTX
- 4 Treatment arms: all receive MMF/Prednisone
  - 1. CSA 150-300 ng/ml x 3 months, then 100-200 ng/ml
  - 2. CSA 50-100 ng/ml
  - 3. TAC 3-7 ng/ml with Daclizumab induction
  - 4. SRL 4-8 ng/ml

At 12 months:

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Acute Rejection (%)</th>
<th>Graft Survival (%)</th>
<th>GFR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSA “standard”</td>
<td>25.8</td>
<td>89.3</td>
<td>57.1</td>
</tr>
<tr>
<td>CSA “low”</td>
<td>24.0</td>
<td>93.1</td>
<td>59.4</td>
</tr>
<tr>
<td>TAC “low”</td>
<td>12.3*</td>
<td>94.2*</td>
<td>65.4*</td>
</tr>
<tr>
<td>SRL “low”</td>
<td>37.2</td>
<td>89.3</td>
<td>56.7</td>
</tr>
</tbody>
</table>

NEJM 2007; 357: 2562-75
## BK virus: treatment options

<table>
<thead>
<tr>
<th>Switch</th>
<th>Decrease</th>
<th>Discontinue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tac to CSA (100-150)</td>
<td>Tac (&lt;6)</td>
<td>Tac or MMF: CSA/Pred</td>
</tr>
<tr>
<td>Tac to SRL (&lt;6)</td>
<td>MMF (&lt;1g/d)</td>
<td>-SRL/Pred</td>
</tr>
<tr>
<td>MMF to AZA</td>
<td>CSA (100-150)</td>
<td>-MMF/Pred</td>
</tr>
<tr>
<td>MMF to SRL (&lt;6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMF to leflunomide</td>
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</tr>
</tbody>
</table>

**Investigational agents:**

- Cidofovir
- Leflunomide
- IVIg
- Fluoroquinolones
Interventions to slow BKV progression: does anything work?

- Possible interventions:
  - Cidofovir 0.25 mg/kg q 2 weeks x 4
  - Transition to CSA (trough 125-175 ng/ml) vs reduction of TAC (4-6 ng/ml) combined with reduction of MMF (250 mg BID)
  - IVIg 1.25 g/kg x 2

- None demonstrated a benefit

Wadei HM et al, Am J Transplant 2006; 6: 1025
In established BKVAN: Immunosuppression Withdrawal (2-drug therapy) Preserves Graft Function Compared to Reduction

Weiss AS et al, CJASN 2008; 3: 1812

No association with graft survival using ancillary therapies (leflunomide, IVIG, or cidofovir)
Leflunomide +/- cidofovir in addition to immunosuppression reduction

- 26 patients with biopsy-proven BKVAN:
- MMF discontinued,
- 17 leflunomide alone
- 9 leflunomide + cidofovir
  - Leflunomide: 100 mg/d x 3, then 20mg/d, goal trough 50-100 ng/ml
  - Cidofovir: 0.25mg/kg IV biweekly x 4 doses

- Still, 4 of 26 lost graft during follow-up

Josephson M et al, Transplantation 2006;81: 74
Unexplained kidney dysfunction >0.3 mg/dl over baseline:
- Check blood BKV PCR as part of workup.

Blood studies (DNA PCR)
- Months 1, 2, 3, 6, 9, 12

Positive urine screen:
- Check blood BKV DNA PCR

Screening asymptomatic (stable) patients for BKV:
- Recommended if estimated prevalence >2%

Urinary studies (DNA PCR, mRNA, or cytology-decoy cell)
- Months 1, 3, 6, 9, 12

Blood BKV PCR >10,000 copies/ml:
- Kidney biopsy for BKV presence and staging
- Consider empiric immunosuppression dose reduction if renal function stable

No BKV identified:
- ("Presumptive BKVAN")
  - Decrease Immunosuppression

BKV and vascular rejection +/- C4d+:
- ("BKVAN and rejection")
  - IVIg, decrease immunosuppression, consider change to leflunomide

BKV +/- tubulitis:
- ("BKVAN, with/without features of cellular rejection")
  - Decrease immunosuppression, consider corticosteroids or IVIg for tubulitis (controversial)

Continue to follow BKV PCR every 2-4 weeks until negative
- Decrease immunosuppression as needed for elevations in BKV PCR titer
- Consider ancillary therapies (cidofovir, leflunomide, IVIg, fluoroquinolones)

BKV Blood PCR negative:
- Consider monitoring for recurrence via blood BKV PCR
- Biopsy for unexplained kidney dysfunction

Wiseman AC, AJKD 2009
ACEI/ARBs for kidney transplant recipients—"value added?"

2031 patients, single center, 1990-2003

10y death-censored graft survival 76% vs 71%

10y patient survival 74% vs 53%

ACEI were not specifically “graft protective” but were associated with reduced mortality

Heinze et al, JASN 2006; 17: 889
Are ACEI/ARBs protective in kidney transplant recipients?

- 17,929 patients, multi-center (107 centers, voluntary database), 1995-2004

Opelz et al, JASN 2006; 17: 3257
Prospective screening for *de novo* HLA Ab: Can this help identify patients at risk for Chronic Allograft Dysfunction?

246 patients transplanted 9/07 to 9/09

- 185 without de-novo DSA
- 61 developed de-novo DSA

*De-Novo DSA detected prospectively in 24.8%

12 in the setting of clinical suspicion (rejection)

49 by protocol screening at 1, 6, 12 months

### HLA MFI

<table>
<thead>
<tr>
<th>All HLA</th>
<th>Total (168)</th>
<th>Average MFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA class I</td>
<td>48 (29%)</td>
<td>1698 (500-7577)</td>
</tr>
<tr>
<td>HLA class II</td>
<td>120 (71%)</td>
<td>3146 (510-11,008)</td>
</tr>
</tbody>
</table>

Cooper JE et al, ATC 2010
# Clinical Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All (246)</th>
<th>No DSA (185)</th>
<th>DSA + (61)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt survival, N (%)</td>
<td>240 (98)</td>
<td>180 (97)</td>
<td>60 (98)</td>
<td>0.58</td>
</tr>
<tr>
<td>GFR 6 mo (236/246 available)</td>
<td>63.75</td>
<td>58.59</td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>GFR 12 mo (177/192 available)</td>
<td>66.51</td>
<td></td>
<td>59</td>
<td>0.04</td>
</tr>
<tr>
<td>Rejection, N (%)</td>
<td>34 (14)</td>
<td>17 (9)</td>
<td>17 (28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>-AMR</td>
<td>5/34 (15)</td>
<td>0</td>
<td>5/61 (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>-Cellular</td>
<td>29/34 (85)</td>
<td>17/185 (9)</td>
<td>12/61 (20)</td>
<td>0.03</td>
</tr>
<tr>
<td>Graft survival (death censored), N (%)</td>
<td>237 (96)</td>
<td>181 (98)</td>
<td>56 (92)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*De novo* Donor-Specific HLA Ab in the first year was associated with AR, worse GFR, and graft loss

Cooper JE et al, ATC 2010
Outcomes in patients **without** acute rejection:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No DSA (168)</th>
<th>DSA (44)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt survival</td>
<td>163 (97)</td>
<td>44 (100)</td>
<td>0.23</td>
</tr>
<tr>
<td>Graft survival (death censored)</td>
<td>166 (99)</td>
<td>44 (100)</td>
<td>0.47</td>
</tr>
<tr>
<td>GFR 6 mo</td>
<td>64.67</td>
<td>60.3</td>
<td>0.11</td>
</tr>
<tr>
<td>GFR 12 mo</td>
<td>67.14</td>
<td>61.46</td>
<td>0.15</td>
</tr>
</tbody>
</table>

In the absence of clinically identified acute rejection, the development of *de novo* donor specific HLA antibodies was **not** associated with worse graft outcomes.

- Worthwhile to screen asymptomatic patients?
- Follow-up time too short?

Cooper JE et al, ATC 2010
The CONVERT study: Can CNIs be withdrawn later after transplant to preserve renal function?

Mean of 3.2 years after kidney transplantation

* Concomitant medications included mycophenolate mofetil (MMF) or azathioprine (AZA), and corticosteroids
* 93% of patients in the SRL arm and 88% of patients in the CNI arm had CAN≥1

Late conversion from CNI to SRL: no benefit, potential for harm

(ITT Analysis, baseline GFR > 40 mL/min)

<table>
<thead>
<tr>
<th></th>
<th>SRL conversion</th>
<th>CNI continuation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 month eGFR (mL/min)</td>
<td>59.0</td>
<td>57.7</td>
<td>0.28</td>
</tr>
<tr>
<td>24 month eGFR (mL/min)</td>
<td>53.7</td>
<td>52.1</td>
<td>0.30</td>
</tr>
</tbody>
</table>

• Late conversion to a sirolimus-based regimen showed no renal function benefit, with worsening proteinuria
  – Release of CsA-induced afferent arteriolar vasoconstriction\(^1\), antagonism of VEGF\(^2\), loss of nephrin expression with mTOR\(^3\) are potential mechanisms

“Late” CNI Withdrawal with MMF/Pred maintenance in chronic allograft dysfunction

122 subjects with allograft dysfunction (CAN or CNI toxicity) placed on MMF and CNI withdrawn (n=62) or remained on CsA (n=60)

CrCl (ml/min)

Run-in/Phase I

Phase II

Phase III

Weeks

Baseline 5 10 18 26 34 42 50 58

CsA MMF

Dudley C et al, Transplantation 2005;79: 466
Not all IF/TA is created equal?

- DeKAF study of 337 patients with “new onset late graft survival” undergoing biopsies:
  - Inflammation in areas of tubular atrophy (“iatr”) was associated with decreased graft survival
  - Does this reflect alloimmune response?

Mannon R et al, Am J Transplant 2010; 10: 2066
Management of allograft fibrosis: from theory to practice?

Chemokine antagonists?
Block TGF-β pathway?
Block epithelial mesenchymal transition?
Conclusions

• Chronic allograft dysfunction/failure is a multifactorial process, but predominant features/etiologies can be identified

• Unfortunately, both nonspecific and specific treatment strategies are not clearly helpful once an injury pattern has been declared

• Prevention of injury is the focus of current management, while treatment of chronic injury remains an area of active investigation