Pathology an Management of Chronic Allograft Dysfunction

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PLAN

- To review the description of chronic allograft dysfunction (NOT “CAN” or “chronic rejection”)
- To review the “Banff 2007 Update”
- To review the causes of chronic allograft dysfunction
- To review the potential treatment modalities of chronic allograft dysfunction/failing kidneys
Case Discussion

- 21 year old African American woman
- ESRD due to lupus nephritis (class V)
- Living donor transplant
- Microscopic hematuria, proteinuria (2.7 g/day) and elevated serum creatinine (2.5 mg/dl) six years after transplantation
- Kidney biopsy: Focal proliferative GN with crescents and immune complexes (WHO class III, consistent with SLE)
Case Discussion

• Steroid pulses (250 mg x 3), prednisone 60 mg/d for one month with taper over the next 3 months
• Severe herpes esophagitis and CMV infection
• ACE inhibitor, good blood pressure control, on 1000 mg twice a day of mycophenolate mofetil
• Returned to dialysis 8 years after transplantation-2 years after the biopsy
Chronic Allograft Dysfunction

- Progressive graft failure with slowly rising serum creatinine and decreasing GFR
- End-stage kidney disease from a variety of insults to the graft
- Independent of acute rejection
- Variable degrees of hypertension and proteinuria
- Features of chronic allograft nephropathy: vascular intimal hyperplasia, interstitial fibrosis and tubular atrophy
Causes of Allograft Injury

- **Immunologic (Antigen-dependent)**
  - Cellular immunity
    - Inadequate immunosuppression/noncompliance
  - Humoral immunity
  - Acute rejection
  - HLA-matching
  - **Donor-specific antibodies (DSA)**
- **Infections**
  - Cytomegalovirus (CMV)
  - **BK virus**
Causes of Allograft Injury

- Nonimmunologic (Antigen-independent)
  - Organ viability
    - Living vs deceased
    - Donor age
    - Brain death
  - Prolonged cold ischemia time
    - Ischemia-reperfusion injuries
  - Delayed graft function
    - Delayed graft function/acute tubular necrosis
- Recipient-related factors
  - Hypertension
  - Hyperlipidemia
  - Compliance
  - Obstruction
  - Recurrent disease
- Treatment - nephrotoxicity due to CNIs
Banff 2007 Update

• 1. Normal
• 2. Antibody-mediated changes
  • C4d deposition without morphologic evidence of active rejection
  • Acute antibody-mediated rejection
  • Chronic active antibody-mediated rejection
• 3. Borderline changes: “suspicious” for acute T-cell-mediated rejection
• 4. T-cell-mediated rejection
  • Acute T-cell-mediated rejection
  • Chronic active T-cell-mediated rejection
• 5. Interstitial fibrosis and tubular atrophy (IF/TA)
• 6. Other: Changes not considered to be due to rejection

Solez K, et al. AJT 2008
<table>
<thead>
<tr>
<th>Etiology</th>
<th>Causes of IF/TA (non-rejection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hypertension</td>
<td>Arterial/fibrointimal thickening with reduplication of elastica, usually with small artery and arteriolar hyaline changes.</td>
</tr>
<tr>
<td>CNI¹ toxicity</td>
<td>Arteriolar hyalinosis with peripheral hyaline nodules and/or progressive increase in the absence of hypertension or diabetes. Tubular cell injury with isometric vacuolization.</td>
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<tr>
<td>Chronic obstruction</td>
<td>Marked tubular dilation. Large Tamm–Horsfall protein casts with extravasation into interstitium, and/or lymphatics.</td>
</tr>
<tr>
<td>Bacterial pyelonephritis</td>
<td>Intratubular and peritubular neutrophils, lymphoid follicle formation.</td>
</tr>
<tr>
<td>Viral infection</td>
<td>Viral inclusions on histology and immunohistology and/or electron microscopy.</td>
</tr>
</tbody>
</table>

Table 1: Morphology of specific chronic diseases

Transplant Vasculopathy (TV)

Artery from a vehicle-treated allograft

Artery with TV; NI: neointima; arrowhead: elastin

• Renal allograft biopsy (*silver staining*)

• Evidence of “double contours” in capillary loops

• Mesangial proliferation and matrix expansion and basement membrane thickening

• Renal allograft biopsy with C4d deposition (*in brown*) in peritubular capillaries consistent with antibody-mediated rejection

The Natural History of Chronic Allograft Nephropathy

- A prospective study of 120 recipients with type 1 diabetes, all but 1 of whom had received kidney–pancreas transplants (1987-2000)
- 961 kidney-transplant–biopsy specimens taken regularly from the time of transplantation to 10 years thereafter

Table 1. Characteristics of the Allograft at and after Transplantation.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>At Transplantation† (N=135)</th>
<th>3 Mo (N=138)</th>
<th>6–12 Mo (N=188)</th>
<th>2–5 Yr (N=223)</th>
<th>6–10 Yr (N=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banff score‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Chronic interstitial fibrosis</td>
<td>0.09±0.24</td>
<td>0.70±0.53</td>
<td>1.07±0.56</td>
<td>1.34±0.67</td>
<td>1.64±0.74</td>
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<tr>
<td>Tubular atrophy</td>
<td>0.06±0.20</td>
<td>0.56±0.51</td>
<td>0.99±0.52</td>
<td>1.26±0.67</td>
<td>1.57±0.76</td>
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<tr>
<td>Fibrointimal thickening</td>
<td>0.03±0.16</td>
<td>0.11±0.30</td>
<td>0.17±0.38</td>
<td>0.31±0.51</td>
<td>0.33±0.51</td>
</tr>
<tr>
<td>Chronic glomerulopathy</td>
<td>0.0±0.04</td>
<td>0.08±0.10</td>
<td>0.08±0.26</td>
<td>0.12±0.30</td>
<td>0.24±0.48</td>
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<tr>
<td>Mesangial matrix (mm)</td>
<td>0.09±0.29</td>
<td>0.18±0.41</td>
<td>0.31±0.41</td>
<td>0.44±0.48</td>
<td>0.62±0.57</td>
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<tr>
<td>Arteriolar hyalinosis</td>
<td>0.16±0.35</td>
<td>0.29±0.48</td>
<td>0.39±0.54</td>
<td>0.72±0.71</td>
<td>1.22±0.83</td>
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<tr>
<td>Sclerosed glomeruli (%)</td>
<td>1.7±4.3</td>
<td>2.3±6.2</td>
<td>2.1±4.9</td>
<td>14.1±18.1</td>
<td>37.2±21.9</td>
</tr>
<tr>
<td>Subclinical rejection (%)</td>
<td>NA</td>
<td>41.8</td>
<td>36.8</td>
<td>19.5</td>
<td>12.3</td>
</tr>
<tr>
<td>Isotopic glomerular filtration rate (ml/min)</td>
<td>NA</td>
<td>59.3±16.8</td>
<td>60.7±17.0</td>
<td>54.7±19.8</td>
<td>50.2±27.2</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>NA</td>
<td>1.48±0.61</td>
<td>1.45±0.33</td>
<td>1.56±0.55</td>
<td>1.62±0.48</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. The numbers are the numbers of biopsy specimens. To convert values for serum creatinine to micromoles per liter, multiply by 88.4. NA denotes not applicable.
† Samples were obtained up to one week after transplantation.
‡ Banff scores range from 0 to 3, with higher scores indicating more severe abnormalities.

Identifying Specific Causes of Kidney Allograft Loss

- 1317 kidney recipients at Mayo Clinic
- During 50.3±32.6 months of follow-up: 330 grafts were lost (25.0%)
  - 138 (10.4%) due to death with function
  - 39 (2.9%) due to primary nonfunction
  - 153 (11.6%) due to graft failure censored for death

El-Zoghby ZM, et al. AJT 2009
Identifying Specific Causes of Kidney Allograft Loss

![Pie chart showing causes of kidney allograft loss: 56% Glomerular disease, 31% Fibrosis/atrophy, 12% Acute rejection, 5% Unknown, 16% Medical/surgical.]

El-Zoghby ZM, et al. AJT 2009
Identifying Specific Causes of Kidney Allograft Loss

- In cases with fibrosis/atrophy a specific cause(s) was identified in 81% and it was rarely attributable to calcineurin inhibitor (CNI) toxicity alone (n = 1, 0.7%)
- Contrary to current concepts, most cases of kidney graft loss have an identifiable cause that is not idiopathic fibrosis/atrophy or CNI toxicity
- If sufficient clinical and histologic information is available, most cases of kidney allograft failure can be attributed to a specific cause
Relevant Donor Abnormalities

- Advanced donor age
- Pre-existing disease or injury to the donor: glomerulosclerosis (>20%), microvascular disease
- HLA-mismatch
- Prolonged cold ischemia time
- Living vs deceased donors: ischemia-reperfusion injury
- Using time-zero biopsies: might be very helpful to assess subsequent biopsies
*Delayed graft function (DGF): major predictor of graft failure overall with cold ischemia time (CIT) as an important independent factor

*Prolonged CIT, directly and independently of DGF and AR, compromises the long-term graft survival

HLA-Specific Antibodies Developed in the First Year Posttransplant are Predictive of Chronic Rejection and Renal Graft Loss

Lee, Po-Chang; Zhu, Lan; Terasaki, Paul I.; Everly, Matthew J.

Transplantation 2009

- Retrospective case-controlled study from Taiwan
- 278 patients, transplanted between 1991-2004
- 25 patients with failed graft (230 serum samples) and 25 patients with a functioning graft (305 serum samples)
• HLA antibody development within 1-year posttransplant markedly lowers allograft survival

Lee PC, et al. Transplantation 2009
Hypertension after Kidney Transplantation

- Very common
- Not well controlled—despite multiple antihypertensive medications
- Independent risk factor for graft failure and mortality

Improved Long-Term Outcomes with Blood Pressure Control

- 24,404 patients transplanted between 1987 and 2000-Collaborative Study Database
- Patients whose SBP was >140 mmHg at 1 year posttransplant but controlled to ≤140 mmHg by 3 years had significantly improved long-term graft outcome compared with patients with sustained high SBP to 3 years
- At 5 years : SBP lowering after year 3 was associated with improved 10-year graft survival

Antihypertensives for Kidney Transplant Recipients

- Meta-analysis of randomized controlled trials
- 60 trials, enrolling 3802 recipients
- Twenty-nine trials (2262 patients) compared calcium channel blockers (CCB) with placebo or no treatment
- 10 trials (445 patients) compared ACEi with placebo or no treatment
- 7 studies (405 patients) compared CCB with ACEi
- In direct comparison with CCB, ACEi decreased GFR, proteinuria, hemoglobin, and increased hyperkalemia
- Graft loss data were inconclusive

Cross AN, et al. Transplantation 2009
The use of ACEI/ARB therapy was associated with longer patient and graft survival after renal transplantation (2,031 patients, transplanted 1990-2003)

Risk of Long-Term Graft Loss

- 1505 patients with biopsy-proven GN from Australia (1988-1997)
- Most frequent causes of allograft loss at 10 years: 1. Chronic rejection, 2. Death with a functioning graft, 3. Recurrence
- The incidence of allograft loss due to recurrence at 10 years was 8.4% and increased overtime
- Recurrence is more frequent than acute rejection as a cause of allograft loss during first 10 years after transplant

Briganti EM, et al NEJM 2002
Recurrent Disease (True Recurrence): Diagnosis

Biopsy proven disease on native kidney

↓↓

Posttransplant proteinuria or hematuria or elevated creatinine

↓↓

Same biopsy proven disease on kidney transplant
Recurrent Glomerular Diseases (GN)

- **Recurrent of primary GN**: FSGS, MPGN, IgA nephropathy
- **Recurrent of secondary GN**: SLE, Henoch-Schönlein, HUS/TTP, anti-GBM disease
- **Recurrent of metabolic or systemic disease**: diabetic nephropathy, amyloidosis, scleroderma, oxalosis, Fabry disease
Recurrent GN in the Transplant

- The prevalence of GN as the cause of **ESRD**: 10-25%, higher prevalence in children and white patients
- **The prevalence of recurrent GN**: 1.9%-31% in different series
- **True prevalence of recurrent GN**: patients who lost their grafts due to recurrence + patients who have recurrence with a functioning graft
- **Cause of graft loss**: 1-8.4% of all graft failures
Potential Problems for Identifying Recurrent GN in the Transplant

- Primary disease-native kidney disease-is unknown for many patients
  - Late presentation
  - Primary vs secondary FSGS: difficult to differentiate
- No unified approach for patients with urinary abnormalities and increased serum creatinine after transplantation (histological vs clinical diagnosis)
- Transplant biopsy is not routinely submitted for IF and EM examination
Potential Problems for Identifying Recurrent GN in the Transplant

• Interpretation of the biopsy: DIFFICULT, *de novo* vs recurrent-MPGN vs chronic rejection vs changes already present in the grafted kidney

• Most of the studies are small and retrospective with variable follow-up periods (mostly short-term, inconsistent f/u)

• *No randomized, prospective studies for different treatment regimens (only case reports: MMF promising in some of them)*
Protocol Biopsies

- Processes that lead to late graft loss begin early and can be detected by protocol biopsies (1–3 months).
- Chronic tubulo-interstitial and vascular changes can be seen in one third of transplants after 1 year and at later times become nearly universal.
- Detection of abnormalities in early protocol biopsies (the presence of IF/TA) is predictive of subsequent graft function and loss.
- Biopsies at 3 months scored as Banff ci0 and cv0 have a significantly better graft survival at 5 years.
- Early treatment may have a dramatic effect on the outcome of the graft—No clear treatment options.
Protocol Biopsies

- Role is not clear on managing transplant patients
- Can we identify patients who are at risk of developing graft dysfunction?
- Benefit of this approach has yet to be evaluated in large, multicenter, and prospective trials (efficacy variable in clinical trials)
- Complications—all within 4 hours: gross hematuria 3.5%, perirenal hematoma 2.5%, and A-V fistula with mostly spontaneous resolution 7.5%

Minimizing the Impact of CNI-induced Nephrotoxicity

- CNI avoidance: not very successful in the past
- Conversion: CNI withdrawal at 3-mo or 6-mo; conversion to MMF or sirolimus
- Minimization of CNIs/additional agents: low dose CNI with MMF/MPA ± steroids or mTOR inhibitors
- New agents such as belatacept (a selective costimulation blocker)
Belatacept Studies

- Less diabetes, better BP control, better lipids; very few patients with DSA
- More acute rejection; but better GFR
- PTLD: 8 in MI (6 CNS), 6 in LI (3 CNS), 2 in CsA arm; most of them EBV negative
- Recently approved by the FDA
- Do not use in patients who are EBV negative
Mycophenolate Mofetil (MMF) versus Azathioprine (AZA)

- Systematic review of the literature and meta-analysis (1985-2007)
- Randomized controlled studies
- Direct comparison of MMF vs AZA
- 27 publications from 19 trials included

Knight SR, et al. Transplantation 2009
Mycophenolate Mofetil (MMF) versus Azathioprine (AZA)

- 3143 patients (1775 on MMF vs 1368 on AZA)
- The use of MMF significantly reduced the risk of acute rejection compared with AZA overall
- The hazard of graft loss was lower in the MMF group

Knight SR, et al. Transplantation 2009
Evaluation of a Patient with Late Allograft Dysfunction

- Exclusion of obvious causes such as obstruction, dehydration, high CNI levels, uncontrolled hypertension, and UTI/urosepsis
- Urinalysis, spot urine protein/creatinine ratio, and 24-h urine collection
- BK viral load (blood/urine)
- Kidney biopsy: consider early before significant graft dysfunction
Evaluation of a Patient with Late Allograft Dysfunction

- Adequate biopsy sample to make a correct diagnosis (at least 10 glomeruli and two arteries; two cores of cortex preferably); comparison with time-zero biopsies, if possible
- Light microscopy to assess fibrosis and tubular atrophy, as well as specific stains (PAS and silver stain)
- IF to assess recurrent or de novo GN or C4d deposition
- EM to detect early transplant glomerulopathy or immune deposits
Therapy for Chronic Allograft Dysfunction

- There is no single specific treatment; several therapies and approaches
- Early diagnosis/early intervention: IMPORTANT
- Changes in serum creatinine occur at a late stage
- Serum creatinine might underestimate deterioration in GFR
Therapy for Chronic Allograft Dysfunction

- Minimization of cold ischemia time
- Aggressive management of hypertension: BP goal <130/80 mmHg
  - Use of calcium channel blockers
- Management of diabetes/PTDM
- Treatment of hyperlipidemia-LDL target <100
- Reduction of proteinuria-ACEi/ARB and or spironolactone use
- Treatment of infections-CMV/BK
- Treatment of recurrent diseases
Therapy for Chronic Allograft Dysfunction

- Manipulation of immunosuppression
  - More potent immunosuppressive therapy early after transplantation followed by minimization of immunosuppression, especially CNIs, to avoid CNI toxicity and BK nephropathy
  - Treatment of subclinical rejection
  - Monitoring and removal of HLA antibodies
  - Minimization or elimination of calcineurin inhibitors
  - Use of non-nephrotoxic immunosuppressive agents
  - Tolerance induction strategies
Mission Possible?
BK Nephropathy

- Intranuclear inclusion bodies in epithelial cells and severe tubular injury
- Interstitial fibrosis
- Positive immunohistochemical staining
- Electron microscopy demonstrating viral particles
Screening and Diagnostic Testing for BK

- Linear progression is an opportunity: from viruria (30-40%) to viremia (10-20%) to nephropathy (1-10%) and graft dysfunction/loss
- Blood and/or urine samples every 3 months for first 2 years, then once a year and in the event of allograft dysfunction
- Careful reduction of immunosuppression and close follow-up for development of acute rejection - **No specific antiviral drug treatment**
BK Nephropathy

- The prevalence rate varies from 1% to 10% due to different local immunosuppression protocols and diagnostic approaches

- Pathophysiology:
  - Replicates best in uroepithelial cells, but also found in lymphoid, other tissues
  - Asymptomatic viruria/viremia
  - Ureteral ulceration, stricture & stenosis, hemorrhagic cystitis
  - Progressive loss of renal allograft function
  - Urothelial malignancy & vasculopathy
Recurrent FSGS

- Recurrence rate: 20-50% (difficult because of the focal nature of the distribution of lesions and possible sampling error)
  - Primary vs secondary vs *de novo*-rapamycin related?
  - Familial forms do not recur after transplantation (linked to genes encoding various podocyte-related proteins, such as podocin, alfa-actinin 4 and nephrin)
- In series with primary FSGS and including pediatric patients and young adults: the incidence of recurrence is as high as 50%
Treatment for Recurrent FSGS

- No prospective randomized studies
- Plasmapheresis ± dipyridamole (pre-or post transplant), ~50% relapse after stopping plasmapheresis, less effective in adults
- Pre-transplant plasmapheresis in children
- Plasma protein adsorption
- High-dose cyclosporine, cyclophosphamide
- ACE inhibitors, NSAIDs, rapamycin use (controversial)
Treatment for Recurrent FSGS

- Combination of ACE-inhibitor, an AT 1 receptor blocker and the direct renin inhibitor aliskiren
  \[(Freiberger W, et al. Transpl Int 2009)\]
- Combination of plasmapheresis and rituximab
- Anti-TNF alpha treatment (infliximab then etanercept)
- Galactose (oral or IV): a sugar with high \textit{in vitro} affinity for FSPF in chromatographic studies; a trace amount of galactose blocks or reverses the increase in \(P_{\text{alb}}\)
- High dose of oral steroids, IV cyclosporine followed by oral treatment, PE with 5% albumin replacement until month 9, and ramipril
Screening Protocol Based on BK Viral Load

Treatment of BK Nephropathy

• Multicenter prospective studies are needed:
  • Stratifying histologic grading and renal function
  • Use of viral load for diagnosis
  • Evaluation of different treatment strategies: assessing the possibility of chronic allograft dysfunction due to systematic reduction of immunosuppression
  • Longer follow-up
Early detection and intervention before CAN occurs

- Review CNI dose to avoid nephrotoxicity
- Tailor patient management considering donor, recipient and graft factors
  - HLA match
  - Reduce ischemic injury
  - Maximize graft function
  - Increase surveillance for older donor kidney
- Avoid acute and subclinical rejection episodes
- Manage and monitor co-morbidities
  - Hyperlipidemia
  - Hypertension
  - Diabetes

• Kaplan–Meier survival in patients with or without DSA at rejection diagnosis (p = 0.001; log-rank)

52 patients with acute rejection; 16 (31%) with de novo DSA; median follow-up 27.0±17.4 months post acute rejection; de novo DSA significant risk factor for allograft loss but prompt DSA reduction was associated with improved allograft survival

• Death-censored allograft survival stratified by % reduction in iDSA at 14 days postbiopsy (p = 0.021; log-rank)

Subclinical Rejection (SCR)

- Looking at the predictive value of SCR and/or CAN in protocol biopsies on death-censored graft survival
- Protocol biopsy was done during the first 6 months in stable grafts (n=435 transplants)
- Borderline changes and acute rejection: SCR
- Presence of interstitial fibrosis and tubular atrophy: CAN
- Mean follow-up was 91±46 months
- Biopsies were classified as normal (n=186), SCR (n=74), CAN (n=110) and SCR with CAN (n=65)

Cox regression analysis: SCR with CAN and hepatitis C virus were independent predictors of graft survival

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment Groups</th>
<th>GFR (mL/min)</th>
<th>AR (%)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larson, et al&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Mod-High RAPA</td>
<td>63*</td>
<td>19*</td>
<td>*P=NS vs. standard TAC; Mostly living donors</td>
</tr>
<tr>
<td></td>
<td>Standard TAC</td>
<td>61</td>
<td>14</td>
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<tr>
<td>CAESAR&lt;sup&gt;37&lt;/sup&gt;</td>
<td>CYA Withdrawal</td>
<td>51</td>
<td>38*</td>
<td>*P=0.04 vs. standard CYA;</td>
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<td>CYA Minimization</td>
<td>51</td>
<td>25</td>
<td>*P=0.03 vs. CYA minimization</td>
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<td></td>
<td>Standard CYA</td>
<td>49</td>
<td>28</td>
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<tr>
<td>SYMPHONY&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Low TAC</td>
<td>65*</td>
<td>12*</td>
<td>*P&lt;0.001 vs. others.</td>
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<td>Low CYA</td>
<td>59</td>
<td>24</td>
<td>“Low-medium risk” mostly deceased donor transplants</td>
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<tr>
<td></td>
<td>Low RAPA</td>
<td>57</td>
<td>37</td>
<td>Serious adverse events highest in RAPA group.</td>
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<tr>
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<td>Standard CYA</td>
<td>57</td>
<td>26</td>
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<tr>
<td>Belatacept StudyGroup&lt;sup&gt;18&lt;/sup&gt;</td>
<td>High Belatacept</td>
<td>66*</td>
<td>7</td>
<td>6-month results. *P=0.01;</td>
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<td></td>
<td>Low Belatacept</td>
<td>62&lt;sup&gt;5&lt;/sup&gt;</td>
<td>6</td>
<td>^P=0.04 vs. standard CYA. Monthly IV infusions required for Belatacept.</td>
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<td>Standard CYA</td>
<td>54</td>
<td>8</td>
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<td>FREEDOM&lt;sup&gt;22&lt;/sup&gt;</td>
<td>CS Avoidance</td>
<td>59</td>
<td>32*</td>
<td>*P=0.007 vs. standard CS.</td>
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<td>Early CS Withdrawal</td>
<td>59</td>
<td>26</td>
<td>Blacks underrepresented. CYA-based regimens.</td>
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<tr>
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<td>Standard CS</td>
<td>61</td>
<td>15</td>
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<td>Astellas Steroid Withdrawal</td>
<td>Early CS Withdrawal</td>
<td>59</td>
<td>18*</td>
<td>5-year results. *P=0.04 vs. low CS. More CAN (post hoc). TAC-based regimens</td>
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<td>Group&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Low CS</td>
<td>60</td>
<td>11</td>
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<td>CONVERT&lt;sup&gt;20&lt;/sup&gt;</td>
<td>CNI Conversion to RAPA</td>
<td>63*</td>
<td>16</td>
<td>2-year results. *P=0.009 vs.</td>
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<td>CNI Continuation</td>
<td>60</td>
<td>15</td>
<td>CNI Continuation. Adverse events higher but malignancy lower with RAPA.</td>
</tr>
</tbody>
</table>

Womer K and Kaplan B. Am J Transplant 2009
Why do Patients Reject on Belatacept?

- Low saturation of CD86/CD80
- Presence of memory cells
- T cell activation through other costimulation pathways
- Blockade of negative signaling
- Inhibition of T regulatory cells
Belatacept

- BENEFIT study-phase III: 686 patients; 3-arm, basiliximab induction
  - At Month 12, both belatacept regimens had similar patient/grant survival versus cyclosporine (MI: 95%, LI: 97% and cyclosporine: 93%)
  - Belatacept patients experienced a higher incidence (MI: 22%, LI: 17% and cyclosporine: 7%) and grade of acute rejection episodes
  - 5 PTLD in the belatacept group vs 1 in CsA group

Vincenti F, et al. AJT 2010
Belatacept

- BENEFIT-EXT study-phase III: 578 patients; 3-arm, basiliximab induction
  - Patient/graft survival with belatacept was similar to cyclosporine (86% MI, 89% LI, 85% cyclosporine) at 12 months
  - The incidence of acute rejection was similar across groups (18% MI; 18% LI; 14% cyclosporine)
  - One patient (0.5%) in the belatacept MI group and two patients (1%) in the LI group had PTLD during the 12-month period and one additional patient in each belatacept group developed PTLD after Month 12
  - Four of the five cases involved the central nervous system, and two of five (both of the post-Month 12 cases) had CMV disease
  - No patients on cyclosporine developed PTLD

*Durrbach A, et al. AJT 2010*
Relative Risk of Acute Rejection

Knight SR, et al. Transplantation 2009
Hazard ratio for graft loss including death with a functioning graft

Relative risk of diarrhea

Knight SR, et al. Transplantation 2009
Antihypertensives for Kidney Transplant Recipients

- Meta-analysis of randomized controlled trials
- 60 trials, enrolling 3802 recipients
- Twenty-nine trials (2262 patients) compared calcium channel blockers (CCB) with placebo or no treatment
- 10 trials (445 patients) compared ACEi with placebo or no treatment
- 7 studies (405 patients) compared CCB with ACEi
- In direct comparison with CCB, ACEi decreased GFR, proteinuria, hemoglobin, and increased hyperkalemia
- Graft loss data were inconclusive

Cross AN, et al. Transplantation 2009
*Change in GFR

*Change in proteinuria

The use of ACEI/ARB therapy was associated with longer patient and graft survival after renal transplantation (2,031 patients, transplanted 1990-2003)

Potential Problems for Identifying Recurrent GN in the Transplant

- Primary disease-native kidney disease is unknown for many patients.
- No unified approach for patients with urinary abnormalities and increased serum creatinine after transplantation (histological vs clinical diagnosis).
- Transplant biopsy is not routinely submitted for IF and EM examination.
Potential Problems for Identifying Recurrent GN in the Transplant

- Interpretation of the biopsy: DIFFICULT, *de novo* vs recurrent-MPGN vs transplant glomerulopathy
- Most of the studies are small and retrospective with variable follow-up periods
- No randomized, prospective studies for different treatment regimens
Protocol Biopsies

• Processes that lead to late graft loss begin early and can be detected by protocol biopsies (1–3 months)
• Chronic tubulo-interstitial and vascular changes can be seen in one third of transplants after 1 year and at later times become nearly universal
• Detection of abnormalities in early protocol biopsies (the presence of IF/TA) is predictive of subsequent graft function and loss
• Biopsies at 3 months scored as Banff ci0 and cv0 have a significantly better graft survival at 5 years
• Early treatment may have a dramatic effect on the outcome of the graft—No clear treatment options
Protocol Biopsies

• Role is not clear on managing transplant patients
• Can we identify patients who are at risk of developing graft dysfunction?
• Benefit of this approach has yet to be evaluated in large, multicenter, and prospective trials (?efficacy variable in clinical trials)
• Complications—all within 4 hours: gross hematuria 3.5%, perirenal hematoma 2.5%, and A-V fistula with mostly spontaneous resolution 7.5%

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- Early treatment may have a dramatic effect on the outcome of the graft - **No clear treatment options**.
Treatment of Subclinical Rejection

- 72 patients: randomized to biopsies at 1, 2, 3, 6, and 12 mo (Biopsy group), or to 6- and 12-mo biopsies only (Control group)
- SCR: treated during the first 3 months with methylprednisolone boluses
- Treatment of SCR was associated with a reduced progression of IF/TA at 6 months and better graft function at 2 years
- The prevalence of SCR: 30%-patients were on cyclosporine, azathioprine, and steroids

Protocol Biopsies

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• **Complications**- all within 4 hours: gross hematuria 3.5%, perirenal hematoma 2.5%, and A-V fistula with mostly spontaneous resolution 7.5%

Conversion Studies

- Conversion from cyclosporine to tacrolimus-5 year data (CRAF study): significant improvement in renal function but no impact on patient or graft survival
  
  *Shihab F, et al. Transplantation 2008*

- **Convert** trial: 830 patients, 6-120 mo posttx and receiving cyclosporine or tacrolimus, were randomly assigned to continue CNI (n=275) or convert to sirolimus (n=555)

- At 2 years, SRL conversion among patients with baseline GFR> 40 mL/min was associated with excellent patient and graft survival, no difference in BCAR, increased urinary protein excretion, and a lower incidence of malignancy compared with CNI continuation

  *Schena FP, et al. Transplantation 2009*
BK/JC Virus Infection

- 400 healthy blood donors aged 20-59 years were tested for BKV- and JCV-specific antibodies against virus-like particles
- IgG seroprevalence was 82% (328 of 400 donors) for BKV and 58% (231 of 400) for JCV
- Asymptomatic urinary shedding of BKV and JCV was observed in 28 (7%) and 75 (19%) of 400 subjects, respectively

Impact of Preemptive Reduction of Immunosuppression

- 200 adult renal transplant recipients: randomized to tacrolimus (n = 134) or cyclosporine (n = 66)
- Urine and blood were collected weekly for 16 weeks and at months 5, 6, 9 and 12 and analyzed for BK viral load
- By 1 year, 70 patients (35%) developed viruria and 23 (11.5%) viremia; neither were affected independently by immunos used
- Viruria was highest with TAC-MMF (46%) and lowest with CsA-MMF (13%), p = 0.005

Impact of Preemptive Reduction of Immunosuppression

- Management of immunosuppression:
  - Identification of BK viremia triggered discontinuation of AZA or MMF
  - If viremia failed to clear within 4 weeks, the calcineurin inhibitor dose was tapered to trough CsA levels of 100–200 ng/mL or trough TAC levels of 3–5 ng/mL
- After reduction of immunosuppression, viremia resolved in 95%, without increased acute rejection, allograft dysfunction or graft loss
- No BK nephropathy was observed

BK virus and Pre-Emptive Immunosuppression Reduction 5-Year Results

- A retrospective 5-year review
- 5 year follow up in 97% of patients
- Viremia resolved in 95% of patients with reduction of immunosuppression
- 5-year patient survival 91% and graft survival 84%
- Immunosuppression and viremia did not influence graft survival
- Acute rejection: 12% by 5-years after transplant
- No BK nephropathy-no protocol biopsies

Hardinger KL, et al. AJT 2010
Treatment of BK Nephropathy

• No specific antiviral drug treatment
• Reduction/adjustment in immunosuppression remains the cornerstone
• Cidofovir, leflunomide, quinolones, and intravenous immunoglobulin: no randomized prospective clinical trial
### Table 1. Diagnostic Testing for BK Virus Nephropathy

<table>
<thead>
<tr>
<th>Test</th>
<th>Threshold Value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decoy cells (&gt;10/cytospin)</td>
<td>&gt;10 cells/cytospin</td>
<td>25%</td>
<td>84%</td>
<td>5-20%</td>
</tr>
<tr>
<td>Urine BK virus DNA quantitative PCR</td>
<td>&gt;1 x 10^7 copies/mL</td>
<td>100%</td>
<td>92%</td>
<td>31%</td>
</tr>
<tr>
<td>Blood/plasma BK virus DNA quantitative PCR</td>
<td>&gt;1 x 10^4 copies/mL</td>
<td>100%</td>
<td>96%</td>
<td>50-60%</td>
</tr>
</tbody>
</table>

Abbreviations: PCR, polymerase chain reaction; PVAN, polyomavirus-associated nephropathy.

Wiseman AC. Am J Kid Dis 2009
Minimizing the Impact of CNI-induced Nephrotoxicity

- CNI minimization:
  - The Symphony trial: 1 year follow-up
  - 4 arm study (1589 patients):
    - Daclizumab induction, 2 g MMF, low-dose tacrolimus (target level 3-7) and steroids resulted in better renal function and lower acute rejection and graft loss rates compared with three other regimens: two with low-doses of cyclosporine or sirolimus and one with no induction and standard cyclosporine
  - Similar results at additional 2-year follow-up (958 patients)

Ekberg H, et al. AJT 2009
<table>
<thead>
<tr>
<th>End Point</th>
<th>Standard-Dose Cyclosporine (N = 390)</th>
<th>Low-Dose Cyclosporine (N = 399)</th>
<th>Low-Dose Tacrolimus (N = 401)</th>
<th>Low-Dose Sirolimus (N = 399)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end point</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean calculated GFR — ml/min‡</td>
<td>57.1±25.1</td>
<td>59.4±25.1</td>
<td>65.4±27.0</td>
<td>56.7±26.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value for comparison with tacrolimus</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>Reference</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean measured GFR — ml/min¶</td>
<td>63.5±25.4</td>
<td>65.3±26.6</td>
<td>69.6±27.9</td>
<td>64.4±28.5</td>
<td>0.04</td>
</tr>
<tr>
<td>P value for comparison with tacrolimus</td>
<td>0.01</td>
<td>0.10</td>
<td>Reference</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Mean calculated GFR — ml/min¶</td>
<td>46.2±23.1</td>
<td>50.2±23.1</td>
<td>54.3±23.9</td>
<td>47.5±26.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value for comparison with tacrolimus</td>
<td>&lt;0.001</td>
<td>0.007</td>
<td>Reference</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Acute rejection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>At 6 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy-proven (excluding borderline values) — %</td>
<td>24.0</td>
<td>21.9</td>
<td>11.3</td>
<td>35.3</td>
<td>&lt;0.001</td>
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<tr>
<td>P value for comparison with tacrolimus</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>Reference</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>At 12 mo</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected and treated — %</td>
<td>32.8</td>
<td>29.5</td>
<td>17.2</td>
<td>43.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value for comparison with tacrolimus</td>
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<td>&lt;0.001</td>
<td>Reference</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Biopsy-proven (including borderline values) — %</td>
<td>30.1</td>
<td>27.2</td>
<td>15.4</td>
<td>40.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value for comparison with tacrolimus</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>Reference</td>
<td>&lt;0.001</td>
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</tr>
</tbody>
</table>

New Diagnostic Methods

- Gene and protein expression profiles (peripheral blood, urine and graft)
- Predictors of interstitial fibrosis in biopsies
  - Early phenotypic changes indicative of epithelial-to-mesenchymal transition (*de novo* vimentin expression and translocation of β-catenin into the cytoplasm of tubular cells)


- Validation of these tests in transplant patients—diagnosis of a certain disease and also specific treatment
Figure 2: Long-term kidney graft survival calculated from 3 to 10 years in relation to systolic blood pressure of <140 or ≥140 mmHg at 1 and 3 years posttransplant. The respective 1- and 3-year pressures are indicated to the right of each curve, together with numbers of patients studied.

Figure 4: Relationship of blood pressure profiles examined over 5 years on kidney graft survival from 5–10 years. Systolic blood pressures >140 or ≤140 mmHg at 1, 3 and 5 years posttransplant are indicated for each patient group studied. All patients in this analysis had a SBP of >140 mmHg 1 year posttransplant.

Minimizing the Impact of CNI-induced Nephrotoxicity

• New agents: biologics (belatacept, alefacept, efalizumab) and small molecules (Janus Kinase inhibitors)
  • 218 patients: randomized to intensive or a less intensive regimen of belatacept or cyclosporine
  • All patients received induction with basiliximab, MMF, and corticosteroids
  • At six months, the incidence of acute rejection was similar among the groups: 7% for intensive belatacept, 6% for less-intensive belatacept, and 8% for cyclosporine
  • At 12 months, the GFR was significantly higher with belatacept and chronic allograft nephropathy was less common with belatacept than with cyclosporine

Belatacept Potently and Selectively Blocks T-cell Activation

- LEA29Y (BMS-224818)
- CD80 (B7-1)
- CD86 (B7-2)
- CD28
- MHC
- TCR

- No cell division
- No cytokine production
- Anergy
- Apoptosis
Belatacept Studies

- Less diabetes, better BP control, better lipids; very few patients with DSA
- More acute rejection (up to 22%); but better GFR at 12 months
- PTLD: 8 in MI (6 CNS), 6 in LI (3 CNS), 2 in CsA arm; most of them EBV negative
- Despite a favorable vote from FDA Advisory Committee (3/2010), FDA did not approve the use of belatacept and requested longer-term clinical data for the product