A Balancing Act:

Immunosuppression in Transplant Medicine

June 12, 2016
1:00 PM – 2:15 PM
Sheraton Boston Hotel
Republic Ballroom

Supported by an educational grant from
Novartis Pharmaceuticals Corporation
Faculty

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Flavio G. Vincenti, MD

Disclosures

- **Research Support:** Alexion; Bristol-Myers Squibb Company; Genentech, Inc.; Immucor; Novartis Pharmaceuticals Corporation
Dr. Teperman has no disclosures to report
Learning Objectives

- Describe the causes of antibody-mediated complications in kidney and liver transplants.
- Implement regular monitoring strategies that can optimize appropriate immunosuppression while managing side effects in transplant patients.
- Engage transplant patients to become participants in their treatment to promote adherence to medications and improve outcomes.
Agenda

1:15 – 1:20 PM  Introductions
1:20 – 1:30 PM  The Causes of Allograft Failure
1:30 – 1:45 PM  Balancing Immunosuppression Levels to Optimize Care
1:45 – 1:55 PM  Engaging Patients to Improve Adherence and Care
1:55 – 2:05 PM  Applying Novel Technology To Transplant Medicine
2:05 – 2:15 PM  Q&A/Conclusions
The Challenges of Antibody-Mediated Rejection
Two Patients with Antibody Mediated Rejection

**Chart: Avery Jackson**

- **Patient:** 40 year old African American female

- **Medical History:**
  - IgA Nephropathy
  - ESRD
  - Donor: Husband
  - Clinical: Acute Renal Failure
  - Tissue: Injury (morphology)
    - Deposition (immunostatin)

- **Recent Renal Transplant:**
  - 4 days ago
  - Diagnosis: Acute AMBR

- **Characterized by:**
  - Tissue: Injury deposition
  - Serum: DSA

**Chart: Russell Washington**

- **Patient:** 60 year old Caucasian male

- **Medical History:**
  - ESRD
  - Clinical: Acute Renal Failure
  - Tissue: Injury (morphology)
    - Deposition (immunostatin)

- **Renal Transplant:**
  - 6 years ago
  - Diagnosis: Chronic AMBR

- **Characterized by:**
  - Tissue: Injury deposition
  - Serum: DSA

- **History of poor adherence to immunosuppresant medications**
Which of these patients has a better prognosis for allograft survival?

A. Avery (acute AMR)
B. Russell (chronic AMR)
C. Both patients
D. Neither patient
## Early vs. Late AMR In Renal Transplant Recipients

<table>
<thead>
<tr>
<th></th>
<th>Early AMR</th>
<th>Late AMR (Chronic AMR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main risk factor</strong></td>
<td>Positive panel reactivity antibody before transplantation, including factors causing sensitization</td>
<td>Withdrawal or reduction of immunosuppressants. Noncompliance with immunosuppressive therapy, young age</td>
</tr>
<tr>
<td><strong>Antibody</strong></td>
<td>Mostly pre-existing donor-specific antibodies</td>
<td>Mostly de novo donor-specific antibodies, especially HLA class-II antibodies</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td>Very rapid graft dysfunction, significantly decreased urine output, and rapid graft dysfunction</td>
<td>Proteinuria, hypertension, progressive functional deterioration, and overt graft failure</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>ATN-like minimal inflammation; capillary and or glomerular inflammation and/or thrombosis; arterial—v3</td>
<td>May have chronic tissue injury, such as glomerular double contours, peritubular capillary basement membrane multilayering, interstitial fibrosis/tubular atrophy, and/or fibrous intimal thickening in arteries</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Treatment available but prognosis affected</td>
<td>Not reversible by treatment</td>
</tr>
</tbody>
</table>

Transplant Glomerulopathy (Late AMR)

- **Incidence**
  - 4% of protocol biopsies at 1 year
  - Up to 20% at 5 years
  - 22% of patients with DSA
  - 45% of patients with acute AMR

Transplant Glomerulopathy is Strongly Associated With Graft Loss

Multivariate Cox analysis of factors related to the development of TG

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR (CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute antibody-mediated rejection</td>
<td>5.093 (2.77-9.37)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Anti-HLA-II NV</td>
<td>1.860 (1.36-2.54)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Anti-HLA-II DSA</td>
<td>3.195 (1.43-7.15)</td>
<td>.005</td>
</tr>
<tr>
<td>HLA mismatches</td>
<td>.437</td>
<td></td>
</tr>
<tr>
<td>Transplant number</td>
<td>.292</td>
<td></td>
</tr>
</tbody>
</table>

DSA = donor-specific activity; GFR = glomerular filtration rate; HR = hazard ratio; NV = normalized value; TG = transplant glomerulopathy.

Evidence for Antibody-Mediated Injury as a Major Determinant of Late Kidney Allograft Failure

- 173 subjects transplanted before October 1, 2005 (mean time after transplant) 7.3 ± 6.0 years) had a baseline serum creatinine level of 1.4 ± 0.3 mg/dL before January 1, 2006 and underwent biopsy for new onset graft dysfunction after that date (mean creatinine at biopsy 2.7 ± 16 mg/dL).

Antibody-Mediated Injury Compromises Long-Term Renal Allograft Survival: Results from the DeKAF Study

Entry biopsy 7.3 ± 6.0 Years Posttransplant

Graft Survival (%)

Months From Entry Biopsy

- C4d– /DSA–
- C4d– /DSA+
- C4d+ /DSA–
- C4d+ /DSA+

Logrank = 23.20
P = 0.0000

The Role of Antibody-Mediated Rejection and Nonadherence in Kidney Transplant

Distribution of Attributed Causes of Failure
Almost Half of Antibody-Mediated Rejection (ABMR) is Due to Nonadherence

- ABMR 50%
- Polyoma virus nephropathy 7%
- Medical/Surgical conditions 11%
- Glomerulonephritis 18%
- Probable ABMR 9%
- Mixed rejection 5%
- 64% ABMR, probable ABMR, or Mixed rejection
- Non-adherence 47%
- Adherence 53%

N = 315
Impact of Donor Specific Antibodies (DSA) on Outcome

- Patients with DSA have higher rates of antibody mediated rejection
- Patients with acute rejection who develop DSA have worse outcome
- Patients with antibody mediated rejection develop transplant glomerulopathy
- Patients who develop transplant glomerulopathy have worse outcome
What About AMR in Liver Transplants?
Evidence for Hyperacute Rejection of Human Liver Grafts: The Case of the Canary Kidneys

- Sequential liver and kidney transplantation from the same donor was performed in 2 patients
  - The kidney in Patient 1, which was transplanted after the liver, was hyperacutely rejected and removed 6 hours later
  - In Patient 2, who had a strongly positive cytotoxic cross-match with his donor, the liver suffered a massive but reversible injury, while the kidney never functioned

- The kidneys in these cases had served like the canaries which miners once used to detect a hostile environment.

Antibody-Mediated Rejection of Human Orthotopic Liver Allografts

- 51 (24 primary) ABO-incompatible liver grafts were transplanted into 49 recipients

- There was a 46% graft failure rate during the first 30 days for primary ABO-I and 60% for non primary grafts, compared with an 11% graft failure rate for primary ABO compatible (ABO-C), cross-match negative matched patients

- Prominent arterial deposition of antibody and complement components was demonstrated by immunoflourescent staining. Elution studies confirmed the presence of tissue-bound, donor-specific isoagglutininins within the grafts.

- These studies confirm that antibody mediated rejection of the liver occurs

Presentation of acute AMR is otherwise unexplained liver allograft dysfunction
- Falling platelet complement levels
- Increased levels of circulating immune complexes
- Persisted DSA of liver biopsy with microvascular injury in addition to other characteristics commonly associated with allograft rejections.

Proposed Diagnostic Criteria for Chronic Antibody-Mediated Rejection in Liver Allografts

- Paired serum, tissue, and data on 45 matched DSA-positive and DSA-negative recipients of a primary liver-only allograft from January 2000 to April 2009

- Blinded histopathologic evaluation demonstrated that DSA+ versus DSA- patients were more likely to have subtle inflammation and unique patterns of fibrosis, despite normal or near-normal liver function tests

- Propose chronic AMR: (1) DSA, and (2) elimination of other potential causes of a similar injury pattern

Role of Donor-Specific Antibodies (DSAs) in Antibody-Mediated Rejection

- Compared with the kidney, the liver appears to have resistance to AMR. The large size and unconventional sinusoidal microvascular bed of the liver may effectively reduce the relative endothelial damage from DSAs.

- In addition, the secretion of high levels of soluble HLAs and their phagocytosis by sinusoidal Kupffer cells inactivates immune complexes.

- Finally, the liver has a remarkable regenerative capacity following injury.

Challenges In Defining The Roles Of DSAs and AMR in Liver Transplantation

- It occurs but it is a rare event: <1%
- Some experienced clinicians remain skeptical
  - As with any new concept, there is a general reluctance toward its acceptance
  - The majority of patients with DSAs have no evidence of graft dysfunction
  - The liver is inherently protected from this type of graft injury

Treatment of AMR in Liver Transplantation

- There is currently no agreed upon treatment once it occurs
  - Plasma exchange
  - Higher levels of immunosuppression
  - Hepatitis C treatment
  - Re-transplantation

Optimizing and Monitoring Immunosuppression
Many of the drugs currently used require therapeutic drug monitoring (TDM) to assure efficacy and safety.¹

With current treatment regimens, a relatively high proportion of transplant recipients experience underimmunosuppression or overimmunosuppression²

Several promising biomarkers have been identified for determining patient alloreactivity, which help in assessing the risk of rejection and personal response to the drug; others correlate with graft dysfunction and clinical outcome.²

The Challenge of Optimizing Immunosuppression

- Maintaining efficacy
- Preventing DSA
- Preserving GFR
Inflammation Emerging as Another Important Marker of Late Allograft Dysfunction

Current Approaches to Managing Immunosuppression
De novo TAC Minimization with Everolimus: ASSET (A2426) Study Design

De novo Everolimus Facilitates Substantial Tacrolimus Minimization

ASSET: 12 month results

Tacrolimus C0 levels were ~50% lower than in the SYMPHONY study at 12 months¹,²

Low vs. Very Low Tacrolimus with Everolimus: Similar BPAR After Randomization at Month 3

Everolimus and Very Low Tacrolimus: Less CNI Exposure, Better Preservation of Renal Function


ASSET: 12-month results

Δ = 5.34

P = ns
Belatacept and Long-Term Outcomes in Kidney Transplantation

Flavio Vincenti, M.D., Lionel Rostaing, M.D., Ph.D., Joseph Grinyo, M.D., Ph.D., Kim Rice, M.D., Steven Steinberg, M.D., Luis Gaite, M.D., Marie-Christine Moal, M.D., Guillermo A. Mondragon-Ramirez, M.D., Jatin Kothari, M.D., Martin S. Polinsky, M.D., Herwig-Ulf Meier-Kriesche, M.D., Stephane Munier, M.Sc., and Christian P. Larsen, M.D., Ph.D.

Time to Death or Graft Loss From Randomization to Month 84

Survival Probability

N at risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Month 60</th>
<th>Month 84</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belatacept MI</td>
<td>219</td>
<td>199</td>
</tr>
<tr>
<td>Belatacept LI</td>
<td>226</td>
<td>204</td>
</tr>
<tr>
<td>CsA</td>
<td>221</td>
<td>202</td>
</tr>
</tbody>
</table>

Survival Probability

<table>
<thead>
<tr>
<th></th>
<th>Month 60</th>
<th>Month 84</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bela MI vs. CsA</td>
<td>0.0100</td>
<td>0.0225</td>
</tr>
<tr>
<td>Bela LI vs. CsA</td>
<td>0.0045</td>
<td>0.0210</td>
</tr>
</tbody>
</table>

Estimated Mean GFR Over 84 Months: MEM Without Imputation

**Table: Estimated Mean GFR (95% CI)**

<table>
<thead>
<tr>
<th></th>
<th>Belatacept MI</th>
<th>Belatacept LI</th>
<th>CsA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GFR</td>
<td>Difference vs. CsA</td>
<td>GFR</td>
</tr>
<tr>
<td>Month 12</td>
<td>67.0</td>
<td>14.5</td>
<td>66.0</td>
</tr>
<tr>
<td>Month 36</td>
<td>68.9</td>
<td>20.3</td>
<td>68.9</td>
</tr>
<tr>
<td>Month 60</td>
<td>70.2</td>
<td>23.3</td>
<td>70.3</td>
</tr>
<tr>
<td>Month 84</td>
<td>70.4</td>
<td>25.6</td>
<td>72.1</td>
</tr>
</tbody>
</table>

CsA = cyclosporine A; GFR = glomerular filtration rate; LI = less intensive; MEM = mixed effects modeling; MI = more intensive.

Kaplan-Meier Analysis of Cumulative De Novo DSA Over Time

Acute Rejection


<table>
<thead>
<tr>
<th>Banff grade of acute rejection*, n</th>
<th>Belatacept MI (N = 219)</th>
<th>Belatacept LI (N = 226)</th>
<th>CsA (N = 221)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild acute (IA)</td>
<td>7 (3.2)</td>
<td>4 (1.8)</td>
<td>6 (2.7)</td>
</tr>
<tr>
<td>Mild acute (IB)</td>
<td>3 (1.4)</td>
<td>8 (3.5)</td>
<td>7 (3.2)</td>
</tr>
<tr>
<td>Moderate acute (IIA)</td>
<td>18 (8.2)</td>
<td>17 (7.5)</td>
<td>7 (3.2)</td>
</tr>
<tr>
<td>Moderate acute (IIB)</td>
<td>22 (10.0)</td>
<td>10 (4.4)</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>Severe acute (III)</td>
<td>3 (1.4)</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

For patients with an event, the time to event was defined as minimum of event date and date of last dose (transplant date for non-treated patients) plus 56 days. For patients without an event, the time to event was defined as last follow-up date for on-treatment patients, date of last dose plus 56 days for off-treatment patients, and transplant date plus 56 days for non-treated patients. Between Month 36 and Month 84, 0 belatacept MI-treated, 1 (grade IIA) belatacept LI-treated, and 2 (grade IA [n=1], grade IIA [n=1]) CsA-treated patients experienced acute rejection.

*Three patients (n=1 [grade IIA], belatacept MI; n=2, CsA [n=1, grade IA; n=1, grade IIA]) experienced acute rejection more than 56 days after treatment discontinuation.
Why Belatacept Has Not Fulfilled Its Potential as a Transformational Immunosuppression Agent

- Higher rejection rates and histologically more severe
  - Better regimens
- PTLD
  - Not an issue with EBV + recipients and lower acute rejection
- IV administration
  - Could be advantageous for adherence
- Cost
  - Cost-effectiveness yet to be determined
Can Intragraft Inflammation be Treated?

- Can we improve current immunotherapy to suppress inflammation?
- Need novel approaches:
  - CTOT-19 use of infliximab to inhibit early inflammation in kidney transplant patients
  - CTOT-21 adoptive T-reg cell infusions to control graft inflammation
  - Use of anti-IL6 receptor antibody to control inflammation in kidney transplantation

Immunosuppression and Monitoring Considerations in Liver Transplantation
Data from a registry of patients with end-stage renal disease were reviewed in order to estimate the cumulative incidence of chronic renal failure and associated risk among 69,321 persons who received nonrenal transplants in the US between 1990 and 2000.

At 36 months, chronic renal failure developed in 11,426 patients (16.5%).

Of these patients, 3,297 (28.9%) required maintenance dialysis or renal transplantation.

Liver Transplant Patients are at a High Risk of Renal Failure

Cumulative incidence of CRF (%)

<table>
<thead>
<tr>
<th></th>
<th>Time posttransplant (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
</tr>
<tr>
<td>Intestine</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td></td>
</tr>
<tr>
<td>Heart-lung</td>
<td></td>
</tr>
</tbody>
</table>

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Heart-lung</th>
<th>Heart</th>
<th>Intestine</th>
<th>Liver</th>
<th>Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td>576</td>
<td>24024</td>
<td>228</td>
<td>36849</td>
<td>7643</td>
</tr>
<tr>
<td>12</td>
<td>375</td>
<td>19885</td>
<td>152</td>
<td>28495</td>
<td>5633</td>
</tr>
<tr>
<td>24</td>
<td>295</td>
<td>17238</td>
<td>110</td>
<td>24041</td>
<td>4316</td>
</tr>
<tr>
<td>36</td>
<td>219</td>
<td>14687</td>
<td>84</td>
<td>19508</td>
<td>3184</td>
</tr>
<tr>
<td>48</td>
<td>194</td>
<td>12341</td>
<td>57</td>
<td>15724</td>
<td>2327</td>
</tr>
<tr>
<td>60</td>
<td>156</td>
<td>10022</td>
<td>33</td>
<td>12564</td>
<td>1629</td>
</tr>
<tr>
<td>72</td>
<td>133</td>
<td>7997</td>
<td>23</td>
<td>9844</td>
<td>1136</td>
</tr>
<tr>
<td>84</td>
<td>107</td>
<td>6104</td>
<td>13</td>
<td>7345</td>
<td>745</td>
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<tr>
<td>96</td>
<td>72</td>
<td>4526</td>
<td>8</td>
<td>5292</td>
<td>468</td>
</tr>
<tr>
<td>108</td>
<td>46</td>
<td>3096</td>
<td>5</td>
<td>3614</td>
<td>258</td>
</tr>
<tr>
<td>120</td>
<td>30</td>
<td>1991</td>
<td>5</td>
<td>2261</td>
<td></td>
</tr>
</tbody>
</table>

CRF = chronic renal failure

Chronic CNI Therapy Decreases Renal Function

The elephant in the room
Chronic CNI Therapy Decreases Renal Function Over Time In Liver Transplant Recipients

Renal function by stage of kidney disease in liver transplant patients (n = 1502)

<table>
<thead>
<tr>
<th>Stage of Kidney Disease</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>Before Liver Transplantation, % (n)</th>
<th>After Liver Transplantation, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 Month</td>
</tr>
<tr>
<td>1</td>
<td>≥90</td>
<td>54.3 (819)</td>
<td>15.9 (240)</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>34.9 (526)</td>
<td>36.4 (549)</td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
<td>9.5 (143)</td>
<td>43.9 (662)</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>1.1 (17)</td>
<td>3.5 (53)</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 and HD</td>
<td>0.2 (3)</td>
<td>0.3 (4)</td>
</tr>
</tbody>
</table>

Can Experiences in Kidney Transplantation Inform Liver Transplantation?

Demographic characteristics cannot be modified and current trends will probably continue.

Therefore, can we modify immunosuppression?
Most patients currently receive a CNI after liver transplant, similar to the situation in kidney transplantation.

So, are there lessons to be learned from the kidney transplant setting?

CNI = calcineurin inhibitor
Immunosuppressive regimen is highly important after kidney transplant: CNI nephrotoxicity is almost universal

mTORis act via a different signalling pathway to CNIs and have potent immunosuppressive effects via inhibition of T-cell expansion, proliferation and migration

Early rather than late conversion to an mTORi immunosuppressive regimen is more beneficial in preserving renal function

Everolimus with CNI minimization has been investigated in several trials of kidney transplant recipients in relation to efficacy and renal function

mTORi = mammalian target of rapamycin inhibitor

Calcineurin Inhibitor-Free Mycophenolate Mofetil/Sirolimus Maintenance in Liver Transplantation
The Randomized Spare-the-Nephron Trial

- First mTor used in liver transplantation
- Improved renal function
- Intolerability

A multicenter, open-label, randomized, controlled study to evaluate the efficacy and safety of EVR to eliminate or reduce TAC in de novo liver transplant recipients.

Enrollment into TAC-WD arm was stopped due to higher rejection rates and protocol was amended based on DMC recommendation (Apr 2010)

AR = acute rejection; BL = baseline; C0 = concentration; CS = corticosteroids; d = day; EVR = everolimus; HCV = hepatitis C virus; M = month; MMF = mycophenolate mofetil; LTx = liver transplantation; RND = randomization; RFct = renal function; TAC = tacrolimus.

H2304: Significantly Better Renal Function with EVR + rTAC vs TAC-C is Observed 2M After Transplantation and Was Sustained Until 24 Months

H2304: 24-month analysis of the ITT population

Mean eGFR (MDRD [mL/min/1.73m²])

- EVR+rTAC
  - N = 245
  - *p-value < .001
  - †p-value = .001

- TAC-C
  - (N = 243)

eGFR = estimated glomerular filtration rate; EVR = everolimus; ITT = intent-to-treat; LTx = liver transplantation; M = month; MDRD = Modification of Diet in Renal Disease; rTAC = reduced tacrolimus; TAC-C = tacrolimus control.

H2304: The Difference in Renal Function is Even More Pronounced in Patients Who Remained On-Treatment

H2304: 24-month sub-analysis for patients who remained on-treatment

- **EVR+rTAC**
  - N = 245
- **TAC-C**
  - (N = 243)

- *p-value < .0001
- †p-value = .0002

---

**Mean eGFR (MDRD [mL/min/1.73m²])**

- **eGFR** = estimated glomerular filtration rate; **EVR** = everolimus; **LTx** = liver transplantation; **MDRD** = Modification of Diet in Renal Disease; **M** = month; **rTAC** = reduced tacrolimus; **TAC-C** = tacrolimus control

**H2304 Study: Conducted to Address Key Unmet Needs in Liver Transplant Recipients**

Everolimus is an efficacious immunosuppressant that allows for substantial dose reduction of CNIs to preserve renal function.

Everolimus is approved for use in adult kidney transplantation with reduced-dose cyclosporine for patients at low-moderate risk.

H2304 is the largest liver transplant study conducted to date.

Based on H2304 results, everolimus became the only mTORi* approved for use in adult liver transplantation by the EHA and the US FDA.

Protecting Renal Function Following Liver Transplant Requires a Multifactorial Approach

- Optimized perioperative management including fluid management
- Avoiding nephrotoxic drugs
- Biological agents for induction or maintenance
  - ATG, basiliximab
- Immunosuppressive regimens
  - Reducing
  - Delaying
  - Withdrawing
  - Avoiding
    - Calcineurin inhibitors
- Replacement options
  - Mycophenolate
  - Everolimus

ATG = anti-thymocyte globulin

Calcineurin inhibitors
Chart: Lilly Chang

Patient: 65 year old Asian female

Clinical Workup

Presentation:

3cm hepatocellular carcinoma

- 5'1", 90 lbs
- Moderate ascites
- Creatinine is 3
- MELD Score is 35
What immunosuppression would you use initially?

A. CNI inhibitor
B. Everolimus
C. Basiliximab alone
D. Basiliximab with mycophenolate mofetil and steroids
What immunosuppression would you use for maintenance?

A. High dose CNI
B. Moderate dose CNI
C. Everolimus therapy with low dose CNI
D. Belatacept
The Challenges of Adherence
HTN since age 11
Lifelong history of chronic kidney disease
Diagnosed with ESRD in early 20's.
Bilateral nephrectomy at age 25.
Dialysis for 2 years and kidney transplant at age 27.

-5'7", 130 lbs
-BP, 150/90mm Hg

**Current medications**
Calcineurin inhibitor
Mycophenolic acid
Prednisone
Lisinopril

**Current life situation**
Lives with and cares for mother
Part-time job as bookkeeper
Attending graduate school for MBA

Describes busy schedule and often forgets to take medications
Missed last lab appointment for blood work

**Reported medication side-effects**
Intermittent stomach problems
Occasional headaches
One of the most significant self-reported factors for patient nonadherence has been shown to be:

A. Medication side effects
B. Complexity of dosing
C. Lack of social support
D. Poor memory
Self-Reported Nonadherence to Immunosuppressants

- Renal transplant recipients (N = 250)
  - 46% adherent
  - 48% reported timing deviations
  - 18% nonadherent in last 4 weeks

Most significant factor for nonadherence was lack of social support ($p = .022$)

Use of Drug Level Monitoring (Intra-Patient Variability) to Assess Under-immunosuppression/Adherence

356 patients, measured tacrolimus variability while on stable dose ("tacSD" = tacrolimus standard deviation), median follow-up 3.72 years

Composite end point: late allograft rejection, transplant glomerulopathy, or graft loss (including death)

For every 1-unit increase in TacSD, a 27% increase in composite end point [HR 1.27 (95% CI 1.03-1.56)]

Nonadherence to Post-Transplant Immunosuppression

- Study to identify adult patients most at risk for non-adherence (N = 572)
- Over 10 years, 50% reported non-adherence
- Non-adherence was reported highest in the 2-5 year post-transplant phase (56%)
- The highest immune-suppressant nonadherence rates
  - Divorced (76%)
  - History of substance or alcohol use (61%)
  - Mental health needs (60%)
  - Those who missed clinic appointments (83%)
  - Did not maintain medication logs (58%)

Engage Patients to Improve Adherence

- Patients have different barriers to medication adherence
  - Side effects, complex dosing regimens, work schedules, forgetfulness, life circumstances
- Discuss and tailor interventions to individual risk factors
- Encourage support groups – local or online
- Suggest technologies to assist in adherence (reminder systems, etc)

Using New Technology to Improve Outcomes

- Adherence
- Molecular-based diagnosis
- Facilitating Cell Therapy
Technology and Adherence

New approaches to medication adherence include sensor chips that can be incorporated into any pill and signal when a pill has been ingested.

Adherence Efforts Go High-Tech

Social media, mobile apps and other technologies may help patients with medication adherence and self-management skills, and improve outcomes.

Apps for Information and Adherence

- National Kidney Foundation Apps
- General information, dietary information, reminders
- Links to online and local support groups

Technology to Assist with Adherence

The **ingestible sensor** is technology you swallow. It's made entirely of ingredients found in food and activated upon ingestion. You take it alongside your medications, capturing the exact time of ingestion.

Your **body** powers the ingestible sensor. With no battery and no antenna, your stomach fluids complete the power source and your body transmits the unique number generated by the sensor.

The **patch**, body-worn and disposable, captures and relays your body's physiologic responses and behaviors. It receives information from the ingestible sensor, detects heart rate, activity, and rest, and sends information to your mobile device.

Using a Bluetooth-enabled device – like the one you already carry in your pocket or purse – you can access secure **applications** that display your data in context and support care in a variety of different ways.

Ingestible sensors alert doctors when a pill is taken

**Powered by you**

Social Media to Aid Adherence

Health tips, reminders, support groups, Q&A

- Fox Chase Cancer Center
  - YouTube instructional videos
- Penn Medicine
  - YouTube videos, discussion forums
- St. Joseph’s Hospital and Medical Center in Phoenix
  - Twitter for tip of the day
- The University of Maryland Medical Center
  - Twitter, Facebook, YouTube

Improved Adherence via Mobile Technology

- Facilitating active participation in self-care remains an important goal in the current health care and patient community
- Technology-based approaches represent a promising way to address non-participation in adolescent patients
- Cellphones, text messaging, and internet-based tools are widely used in the adolescent population among all socio-economic groups
- Improved adherence and outcomes for pediatric liver transplant recipients by using text messaging

The Use of Precision Medicine

Is it time to introduce it in transplantation?
kSORT (Kidney Solid Organ Response Test) Rejection

Application of the kSORT blood assay for the non-invasive prediction of histological
kSORT Validated in Pediatric and Adult Populations, LD and DD Recipients; Independent of Rx

The kSORT Assay to Detect Renal Transplant Patients at High Risk for Acute Rejection: Results of the Multicenter AART Study

Silke Roedder1, Tara Sigdel1, Nathan Salomonis23, Sue Hsieh1, Hong Dai3a, Oriol Bestard4, Diana Metes5, Andrea Zeevi5, Albin Grisch6, Jennifer Cheeseman7, Camila Macedo5, Ram Peddy3, Mara Medeiros8, Flavio Vincenti1, Nancy Asher1, Oscar Salvatierra9, Ron Shapiro5, Allan Kirk7a, Elaine Reed8, Minnie M. Sarwal12

N = 558 biopsy matched blood samples profiled by QPCR
8 programs; US, EU, Mexico
ADULT and PEDS

A Peripheral Blood Diagnostic Test for Acute Rejection in Renal Transplantation

L. Li1,b,f, P. Khatri1,h, T. K. Sigdel1,b,f, T. Tran1,b, L. Yingb, M. J. Vitalize1,b, A. Chena,b, S. Hsieh1,b, H. Dair5,b, M. Zhanga,b, M. Naesensb, V. Zarkhinb, P. Sansanwalb, R. Chenb, M. Mindrinod, W. Xiaob, M. Benfield1, R. B. Etteneger2, V. Dhamidharkab, R. Mathias1, A. Portale1, R. McDonaldk, W. Hamon1, D. Kershawm, V. M. Vehaskari4, E. Kami4, H. J. Baluarte8, B. Waradyd, R. Davisd, A. J. Butt8, O. Salvatierrabd, and M. M. Sarwal1b,f

study from 12 US pediatric transplant programs. A total of 367 unique human PB samples, each paired with a graft biopsy for centralized, blinded phenotype classification, were analyzed (115 acute rejection (AR), 18C stable and 72 other causes of graft injury). Of the differentially expressed genes by microarray, Q-PCR analysis of a five gene-set (DUSP1, PBEF1, PSEN, MAPK, and NKTR) classified AR with high accuracy. A logistic regression model was built on independent training set (n = 47) and validated on independent test-set (n = 196) samples, discriminating AR from STA with 91% sensitivity and 94% specificity and AR from all other non-AR categories with 91% specificity and 91% sensitivity.}

The answer in a drop of blood.....

17 gene PCR test measuring graft immune activation by RNA isolated from whole blood

CFLAR, DUSP1, IFNGR1, ITGAX, MAPK9, NAMPT, NKTR, PSEN1, CEACAM4, EPOR, GZMK, RARA, RHEB, RXRA, SLC25A37, RNF130, RYBP

K-SORT Analysis

Facilitating Cell Therapy

- The experimental Facilitating Cell Therapy involves taking stem cells from the kidney donor and grafting them into the transplant recipient’s bone marrow at the time of transplant.

- The hematopoietic stem cell-based immunological tolerance protocol is in the final stages of a successful FDA Phase II clinical trial in living donor kidney transplant recipients that has resulted in graft survival without the need for lifelong immunosuppression.

Studies in Progress

- **Massachusetts General Hospital**
  - Examine the safety and effectiveness of a combination kidney and bone marrow transplant from a haplo-identical related donor.

- **University of California at San Francisco**
  - Donor-Alloantigen-Reactive Regulatory T Cell (darTreg) Therapy in Liver Transplantation

- **Northwestern University**
  - Immunoregulatory mechanisms might be amplified in subjects with identical HLA

- **Stanford**
  - HSCT in conditioned HLA-identical related kidney recipients

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Antibody-mediated injury can be a major determinant of late kidney allograft failure.

Immunosuppression is a delicate balance and the challenge of optimizing treatment is to:
- Maintain efficacy
- Prevent DSA
- Preserve GFR

Adherence to immunosuppressive therapy remains a problem in transplant medicine.
- Engaging the patient can make a difference.
Questions?
How to Collect Credit for This Activity

Complete the Pre-Survey, Credit Request Form and Evaluation Form found on your table.

Please submit your completed forms to conference staff before you leave in order to receive your credit.
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