Prevention of sensitization: transfusions, nonadherence, and management of a failed allograft

Robert S. Gaston, MD
Director, Comprehensive Transplant Institute
Robert G. Luke Endowed Chair in Transplant Nephrology
University of Alabama at Birmingham
Birmingham, Alabama
I have the following financial relationships to disclose:

Consultant during the past 12 months for: CTI Clinical Trials, Immucor, Novartis, Veloxis
Prevention of sensitization

- DSA’s are the consequence of appropriate immunologic response to foreign antigen
  - Heterologous immunity (broadly)
  - Pregnancy
  - Blood transfusion
  - Previous transplant
Prevention of sensitization

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  - Heterologous immunity (broadly)
  - Pregnancy
  - Blood transfusion
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- Can be directed at MHC (Class I and II) and non-MHC antigens
Serologic MM and presensitization

MFI>2000 131 patients with failed grafts
Prevention of sensitization

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- Development of DSA is attenuated by immunosuppression
CTOT$09: (Tacrolimus Withdrawal in Immune Quiescent, Low-risk, Kidney Transplant Recipients)

Primary Living Donor Transplants

Transplanted, not randomized
N=26
- Withdrawal of Consent 8
- Lost to Follow-up 1
- Ineligible for Randomization 14
- In f when study stopped 3

Consented/Enrolled Subjects
N=52

Transplanted Subjects
N=47

Randomized Subjects
N=21

Tacrolimus Withdrawal
N=14
- 13 completed withdrawal
  - 7/13 Tacrolimus reinstated
  - 1 failed to complete withdrawal
  - ACR, no DSA (N=3)
  - DSA, no ACR (N=2)
  - DR and DQ (N=1)
  - DQ only (N=1)
  - DSA and ACR (N=3)
  - DR and DQ only (N=1)
  - DQ only (N=2)

Standard Therapy
N=7
- No ACR
- 1 DSA (DQ)
- 1 retrospective, pre-rand DSA (DQ)

Pre Transplant Antibody: no DSA, PRA <30%
Rx: Thymo, Tacrolimus, MMF, Prednisone

0 to 6 mo course: No Acute Rejection
6 mo Protocol Biopsy: Normal Histology
6 mo Antibody Screen: No DSA

What predicts DSA?

JASN (2015) ePub

Immunosuppressant minimization is associated with DSA

n = 127 patients (Zeus and CRAD001)

Everolimus (n = 61)

CsA-ME (n = 66)

p=0.048

p=0.036
Nonadherence and DSA

Non-Adherent
72% at 12 years

Adherent
19% at 12 years

p <0.0001

Wiebe et al.  
*Am J Transplant* 15: 2921, 2015
Nonadherence, DSA, and graft failure

Nonadherent: 24%

Post-dnDSA Graft Survival

Follow-up (years)

p<0.0001

Subclinical dnDSA
Clinical dnDSA

24% Nonadherent
90% Nonadherent

IFTA ci3, ct3
TG cg3

Wiebe et al.
Am J Transplant 15: 2921, 2015
Prevention of sensitization

- DSA’s are the consequence of appropriate immunologic response to foreign antigen
- Can be directed at MHC and non-MHC antigens
- Development of DSA is attenuated by immunosuppression
- Not all DSA exerts adverse impact in retransplantation
  - Characteristics of DSA
Impact of DSA on RMM

Impact of Class 2 RMM on outcome

Table 5. Class 2 RMM increase risk for DCGL only in sensitized recipients before second transplant

<table>
<thead>
<tr>
<th>Covariate</th>
<th>HR (95% CI) ACGL</th>
<th>HR (95% CI) DCGL</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RMM</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Class 1 only</td>
<td>0.98 (0.91 to 1.06)</td>
<td>0.97 (0.88 to 1.06)</td>
</tr>
<tr>
<td>Any class 2</td>
<td>1.08 (1.00 to 1.17)</td>
<td>1.11 (1.00 to 1.22)</td>
</tr>
<tr>
<td>Peak PRA at second transplant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRA=0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No RMM</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Class 1 only</td>
<td>0.91 (0.76 to 1.09)</td>
<td>0.98 (0.78 to 1.23)</td>
</tr>
<tr>
<td>Any class 2</td>
<td>0.99 (0.82 to 1.20)</td>
<td>1.07 (0.84 to 1.35)</td>
</tr>
<tr>
<td>PRA&gt;0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No RMM</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Class 1 only</td>
<td>0.97 (0.88 to 1.07)</td>
<td>0.91 (0.81 to 1.03)</td>
</tr>
<tr>
<td>Any class 2</td>
<td>1.11 (1.00 to 1.22)</td>
<td>1.15 (1.02 to 1.29)</td>
</tr>
</tbody>
</table>

Models are adjusted for age, sex, race, cause of ESRD, donor age, donor type, duration of first graft survival, HLA match for second graft, PRA for second graft, induction, immunosuppression, and year of transplant.
Some preformed DSA disappears

<table>
<thead>
<tr>
<th>N=34 (%)</th>
<th>Persistent</th>
<th>Transient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitizing event (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion</td>
<td>58</td>
<td>59</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>67</td>
<td>100</td>
</tr>
<tr>
<td>Previous transplant</td>
<td>92</td>
<td>50</td>
</tr>
<tr>
<td>More than one</td>
<td>67</td>
<td>50</td>
</tr>
<tr>
<td>DSA (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>42</td>
<td>77</td>
</tr>
<tr>
<td>Class II</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>Class I and II</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>iDSA MFI</td>
<td>7241±4407</td>
<td>1757±1317</td>
</tr>
<tr>
<td>sDSA MFI</td>
<td>10605±6388</td>
<td>1912±1442</td>
</tr>
<tr>
<td>Number of specificities</td>
<td>2.1±1.2</td>
<td>1.1±0.3</td>
</tr>
</tbody>
</table>

Predicting DSA persistence in retransplantation

<table>
<thead>
<tr>
<th></th>
<th>Area under the curve</th>
<th>$P$</th>
<th>Sensitivity for a MFI of 1500 (%)</th>
<th>Specificity for a MFI of 1500 (%)</th>
<th>Specificity for a MFI of 3500 (%)</th>
<th>Specificity for a MFI of 5500 (%)</th>
<th>Specificity for a MFI of 5500 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>iDSA</td>
<td>0.932</td>
<td>&lt;0.001</td>
<td>92</td>
<td>60</td>
<td>83</td>
<td>91</td>
<td>58</td>
</tr>
<tr>
<td>sDSA</td>
<td>0.947</td>
<td>&lt;0.001</td>
<td>100</td>
<td>68</td>
<td>83</td>
<td>86</td>
<td>75</td>
</tr>
</tbody>
</table>

Prevention of sensitization

- DSA’s are the consequence of appropriate immunologic response to foreign antigen
- Can be directed at MHC and non-MHC antigens
- Development of DSA is attenuated by immunosuppression
- Not all DSA exerts adverse impact in retransplantation
  - Characteristics of DSA
  - Memory/inflammatory milieu in recipient
Elispot assay of pretransplant T cell reactivity

Inflammatory milieu

(a) sCD30 negative

(b) sCD30 positive

**Survival (%)**

<table>
<thead>
<tr>
<th>Time posttransplant (years)</th>
<th>Patients</th>
<th>Year 3 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without DSA</td>
<td>174</td>
<td>84-3</td>
</tr>
<tr>
<td>With DSA</td>
<td>96</td>
<td>83-1</td>
</tr>
<tr>
<td>Without DSA</td>
<td>57</td>
<td>85-9</td>
</tr>
<tr>
<td>With DSA</td>
<td>58</td>
<td>62-1</td>
</tr>
</tbody>
</table>

**P-values**

- sCD30 negative: P = 0.81
- sCD30 positive: P = 0.003

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- Can be directed at MHC and non-MHC antigens
- Development of DSA is attenuated by immunosuppression
- Not all DSA exerts adverse impact in retransplantation
- Management of the patient with a failed allograft
  - Immunosuppression?
  - Transplant nephrectomy?
Immunosuppressant targeting

- CNI
  - Basiliximab
  - Belatacept
  - mTORi

- Mycophenolate
- Azathioprine

- ATG
- Alemtuzumab
- Steroids
- Cyclophosphamide

- Tocilizumab

- B Cell

- Belimumab
- Rituximab
- Obinutuzumab
- Eculizumab
Anti-humoral therapy is not essential for successful long-term outcomes providing T cells are under complete control.
### Serologic MM and presensitization

MFI>2000  131 patients with failed grafts

<table>
<thead>
<tr>
<th></th>
<th>Adjusted OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunosuppression</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (n=56)</td>
<td>0.90 (0.33, 3.31)</td>
<td>0.84</td>
</tr>
<tr>
<td>Single (n=36)</td>
<td>0.15 (0.05, 0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dual (n=30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 1 year since relisting</td>
<td>3.53 (1.4, 9.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>&gt; 5 years since relisting</td>
<td>8.36 (2.6, 31.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nephrectomy (n=56)</td>
<td>3.42 (1.5, 8.3)</td>
<td>0.004</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>2.01 (0.61, 6.64)</td>
<td>0.253</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1.44 (0.88, 2.74)</td>
<td>0.185</td>
</tr>
</tbody>
</table>
Impact of nephrectomy on DSA
With and without immunosuppression

A

HLA class I DSA

B

HLA class II DSA

Lachmann N et al.
Nephrectomy associated with lower mortality and increased rate of retransplantation

Interaction of nephrectomy and RMM

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<tr>
<th>Covariate</th>
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<tr>
<td>Any RMM</td>
<td>1.13 (1.01 to 1.26)</td>
<td>1.13 (1.00 to 1.29)</td>
</tr>
<tr>
<td>Nephrectomy of first allograft before second transplant, n=1719</td>
<td>0.94 (0.83 to 1.06)</td>
<td>0.97 (0.82 to 1.15)</td>
</tr>
<tr>
<td>No nephrectomy, n=4454</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No RMM, n=1369</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Class 1 RMM alone, n=175</td>
<td>1.13 (0.92 to 1.38)</td>
<td>1.20 (0.94 to 1.54)</td>
</tr>
<tr>
<td>Any class 2 RMM, n=175</td>
<td>1.30 (1.07 to 1.58)</td>
<td>1.41 (1.12 to 1.78)</td>
</tr>
<tr>
<td>No nephrectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No RMM, n=3198</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Class 1 RMM alone, n=701</td>
<td>0.91 (0.81 to 1.03)</td>
<td>0.90 (0.76 to 1.05)</td>
</tr>
<tr>
<td>Any class 2 RMM, n=555</td>
<td>1.04 (0.92 to 1.18)</td>
<td>1.06 (0.90 to 1.25)</td>
</tr>
</tbody>
</table>

Any RMM restricted to Medicare only and first graft failure before 2010

Tinckam et al.  
*J Am Soc Nephrol*  
2016;27:2833
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- Development of DSA is attenuated by immunosuppression
- Not all DSA exerts adverse impact in retransplantation
- Management of the patient with a failed allograft
  - Immunosuppression: YES, if graft in place and candidate for retransplantation
  - Transplant nephrectomy: Only if clinically indicated