Simultaneous Kidney-Liver Transplantation in the Sensitized Recipient

Allan D. Kirk, MD, PhD, FACS
Professor of Surgery and Pediatrics
Scientific Director, Emory Transplant Center
Vice Chair for Research, Emory Department of Surgery
Emory University, Atlanta, Georgia

Take Home Point 1:
Donor specific alloantibodies harm allografts and in particular harm kidneys.

Alloantibodies Harm Allografts

<table>
<thead>
<tr>
<th>Rejection</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Crossmatch</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td>Negative Crossmatch</td>
<td>8</td>
<td>187</td>
</tr>
</tbody>
</table>

p=0.18 x 10^{-29}

“The ethics of transplanting kidneys without prior knowledge of the results of the lymphocyte crossmatch test...can reasonably be expected to be questioned.”

Mechanisms of Antibody Mediated Injury

Endothelium

anti-HLA Ab

C Activation

C1 C4 C3

Donor HLA

Ag up-regulation

Intracellular Signaling

Smooth muscle proliferation and vascular narrowing

Platelet microthrombi

Chemokine production

Adapted from slide of Dr. Peter Nickerson

Donor HLA MAC

C4d C4a + C4b

Prognostic Value of Pre-formed Alloantibody Detection


Predicting Kidney Graft Failure by HLA Antibodies: a Prospective Trial


| Table 4: Kidney transplant patients with 1- year follow-up data. Graft failures and deaths among patient with or without antibody |
|---|---|---|---|---|---|
| | Patients | Death Failure | % Fail | % Death | p |
| Total | 199 | 52 | 5.5% | 10% | 0.18 |
| Post transplant, total | 122 | 21 | 4.0% | 15% | 0.39 |
| Pre transplant, total | 177 | 31 | 4.0% | 9% | 0.0001 |
| Post transplant, anti-HLA | 147 | 16 | 7.0% | 7% | 0.08 |
| Pre transplant, anti-HLA | 196 | 4 | 0.0% | 0% | 0.19 |
| Patients with antibody, total | 357 | 41 | 2.3% | 2% | 0.08 |

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


Actual Graft Survival by de novo DSA status

Although ABMR can have a rapid and overt onset, particularly in settings of prior sensitization, de novo DSA is late to manifest clinically.
• There is ample data showing that alloantibodies are bad.
• There are no rigorous data in humans showing that donor specific alloantibodies are good.
• There are some weak correlative data showing that, based on limited sensitivity for detecting injury or limited follow-up, that antibodies might, in some situations, be benign.

Take Home Point #2:
When it comes to the case of liver transplantation and in particular liver-kidney transplantation...

See Take Home Point #1.

First Description of Liver Adsorption to facilitate a kidney transplant (dogs)

Animal models show that the simultaneous liver grafts lead to a protective phenotype for concomitantly transplanted organs.


Reports of SKLT


Twelve patients:
- Two died of fungemia/generalized sepsis
- One died after 4 months (cause not mentioned) with “good renal function until his death”.
- One patient had primary non-function with “tubular injury but no evidence of humoral mediated injury” and required retransplantation of the kidney.

Four patients with a positive crossmatch due to class I shown in between Liver and Kidney to have converted to a negative crossmatch and underwent successful kidney transplant, all had subsequent cellular rejection treated with OKT3
Reversal of positive crossmatch

<table>
<thead>
<tr>
<th>Patient</th>
<th>Crossmatch</th>
<th>Preformed Antibodies</th>
<th>Positive Crossmatch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pb1</td>
<td>N</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pb2</td>
<td>N</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pb3</td>
<td>N</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pb4</td>
<td>N</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pb5</td>
<td>N</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pb6</td>
<td>N</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pb7</td>
<td>N</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pb8</td>
<td>N</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pb9</td>
<td>N</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pb10</td>
<td>N</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pb11</td>
<td>N</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pb12</td>
<td>N</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pb13</td>
<td>N</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pb14</td>
<td>N</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pb15</td>
<td>N</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pb16</td>
<td>N</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pb17</td>
<td>N</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pb18</td>
<td>N</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pb19</td>
<td>N</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pb20</td>
<td>N</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>


Combined liver–kidney transplantation and the effect of preformed lymphocytotoxic antibodies

Susan L Saidman, Rene J Duquesnoy, A Jake Demetris, Jerry McCauley, Hector Ramos, George Mazariegos, Ron Shapiro, Thomas E Starzl, and John J Fung
Departments of Pathology, Surgery and Medicine, University of Pittsburgh School of Medicine, Pittsburgh

38 Patients: 18 with CsA/Aza/Pred, 20 with FK506/"low dose" pred

Overall survival, 68%


Combined liver–kidney transplantation and the effect of preformed lymphocytotoxic antibodies

Susan L Saidman, Rene J Duquesnoy, A Jake Demetris, Jerry McCauley, Hector Ramos, George Mazariegos, Ron Shapiro, Thomas E Starzl, and John J Fung
Departments of Pathology, Surgery and Medicine, University of Pittsburgh School of Medicine, Pittsburgh

- Sequentially placed kidney allografts may be protected from hyperacute rejection in the presence of donor specific lymphocytotoxic antibodies, but not in all instances.
- Both patient and kidney allograft survival was lower in positive crossmatch (Amos technique, >20% kill = positive)
- Possible association with titer

A Remarkable Conclusion

Preformed lymphocytotoxic antibodies are not an absolute contraindication to combined liver–kidney transplantation, but do appear to have a deleterious effect on long-term graft survival.

Evidence for hyperacute rejection of human liver grafts: the case of the canary kidneys.

Starzl TE, Demetris AJ, Todo S, ET A!

- Transplantation across a positive crossmatch in a 12yo boy with cystinosis.
- Severe hepatic dysfunction that resolved with rescue therapy.
- The kidney never functioned.
- A subsequent kidney that was crossmatch negative functioned well.
A POSITIVE CROSSMATCH IN LIVER TRANSPLANTATION—NO EFFECT OR INAPPROPRIATE ANALYSIS?: A Prospective Study

Hathaway, Mark1; Gunson, Bridget K.; Keogh, Adrian C.; Briggs, David; McMaster, Paul; Neuberger, James M.

- DSA assessed in 207 liver transplant patients and associated with outcome.
- Graft failures occurred in 5 of 24 (21%) crossmatch-positive recipients and in 7 of 172 (4%) crossmatch-negative recipients.
- Graft survival was significantly lower in crossmatch-positive recipients at 1 month after transplant (P=0.0013) but not at 3 months or 1 year.
- Early graft loss were associated with immunological mechanisms, whereas later losses were not directly immune related.

5/7 kidneys worked, one had primary non-function with humoral rejection and one was lost to ABMR within the first week.
- The auxiliary liver was also destroyed in both of these cases.

Successful Combined Partial Auxiliary Liver and Kidney Transplantation in Highly Sensitized Cross-Match Positive Recipients

- 5/7 kidneys worked, one had primary non-function with humoral rejection and one was lost to ABMR within the first week.
- The auxiliary liver was also destroyed in both of these cases.
Antibody-mediated rejection of renal allograft in combined liver–kidney transplant


- Six SLKT who had performed DSA and positive XM (four class I and II DSA, one class I DSA only, one class II only).
- Acute humoral rejection (AHR) of the kidney occurred in 66% (three with both class I and II DSA and one with only class II DSA) of patients.
- In those with AHR, class I antibodies were rapidly cleared (p < 0.01) while class II antibodies persisted (p = 0.25).
- All patients who had humoral rejection of their kidney had preformed anti-class II antibodies.

**Combined Liver-Kidney Transplants: Allosensitization and Recipient Outcomes**

- Transplant Recipients data on CLK performed from 1995 to 2008.
- Defined sensitization as PRA >10% or a positive T-cell crossmatch.
- 2484 CLK recipients with available PRA or TXM information.
- 30% had positive TXM or PRA more than 10%.
- Among those with TXM information, 12% had a positive crossmatch (n=234).
- In univariate analyses, patient (P=0.002) and overall kidney graft survival (P=0.015) were significantly diminished among sensitized patients.
- In multivariable Cox models, allosensitization was independently associated with patient death (adjusted hazard ratio 1.22, 95% CI, 1.04 –1.43) and overall kidney graft loss (adjusted hazard ratio 1.16, 95% CI, 1.00 –1.36).

Class II Alloantibody and Mortality in Simultaneous Liver-Kidney Transplantation


Table 4: Univariate analyses were calculated with all factors with a P < 0.05 for the variable were entered into a multivariate model. The final multivariate model shows that only those factors were significantly associated with a one-year survival and that those included. Class I DSA for the analyses were defined as either posttransplant or in situ.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR</th>
<th>p value</th>
<th>95% CI</th>
<th>Log likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I DSA</td>
<td>1.21</td>
<td>0.014</td>
<td>1.03 - 1.74</td>
<td>5.01</td>
</tr>
<tr>
<td>Preoperative age</td>
<td>0.95</td>
<td>0.004</td>
<td>0.90 - 0.99</td>
<td>2.23</td>
</tr>
<tr>
<td>Donor age</td>
<td>0.90</td>
<td>0.011</td>
<td>0.86 - 0.95</td>
<td>2.71</td>
</tr>
<tr>
<td>Preoperative albuminuria</td>
<td>0.47</td>
<td>0.002</td>
<td>0.28 - 0.76</td>
<td>5.82</td>
</tr>
<tr>
<td>Presence of Class II DSA</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Antibody reactivity</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MLD + 15</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Antibody reactivity</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MLD + 15</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MLD + Induction</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MLD + Induction</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MLD + Induction</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MLD + Induction</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>


Alloantibody in SLK Transplantation

No effect of Preformed Class I DSA on:
- Patient survival
- Liver allograft survival
- Renal allograft survival
- Renal function


Pre-formed Class II DSA and Rejection

Pre-formed Class II DSA and Survival

De Novo Class II DSA and Survival

Differential Clearance by Antigen Specificity
A Few Simple Considerations

- Antibody efficacy is markedly influenced by antigen/antibody density (C1q crosslinking, etc).
- Antibody binding is largely stochastic, influenced by (among other things) serum concentration and target availability.
- For a fixed amount of antibody (pre-formed), a decrease in antigen density leads to more dispersed antibody and a proportionally decreased effector response.
- Similarly, increases in target availability with a fixed amount of antibody, functionally decreases the density of bound.
- Total body capillary surface area is commonly estimated at 1000m² (14m²/Kg)
  - Renal capillary surface area 0.21m²
  - Liver cap surface area 21m²

Summary

- Pre-formed alloantibodies and their associated effector mechanisms damage kidneys, and their presence is indicative of an established memory T and B cell repertoire.
- The liver mollifies the effect of pre-formed alloantibody, but the impact is spectral, not dichotomous, and can potentially be explained solely by simple concepts of spatial reasoning.
- The literature on this topic is sparse, but consistently supports caution when considering SKLT across a positive crossmatch.
- There is no preferred treatment other than avoidance.
- The decision to proceed in this setting ultimately comes down to risk/benefit assessment, but there is no doubt that pre-sensitization leads to worse outcomes for the kidney, the liver and the patient compared to crossmatch negative.
Importance of antigen specificity for complement-mediated lysis by monoclonal antibodies.

Bindon CI, Hale G, Waldmann H.


Study of antibodies with comparable binding affinity versus antigens with comparable antigen density demonstrating significant differences in lytic potential.

- CAMPATH-1 (lytic), major histocompatibility complex class I (lytic) and leukocyte common antigen (poorly lytic)

Postulates inherent differences in C1 activation potential which involve Fc-Fc interactions, Fc-C1r/b2 interactions and a critical C1q stem-arm angle for C1 binding and activation.
Antibody-mediated cell cytotoxicity in a defined system: regulation by antigen, antibody, and complement.

Lustig HJ, Bianco C.

Abstract

The use of a serum-free environment and target cells carrying defined amounts of radionuclide-labeled antigen allowed a quantitative study of the role of antigen, antibody, and complement on antibody-mediated cell cytotoxicity (AMCC). For lysis to occur, a minimum number of antigen molecules must be present on the target cell. 51Cr release from target cells with lower antigen density requires larger concentration of effector cells and antibodies. Target cell-bound complement, itself unable to mediate cytotoxicity, reduces the number of IgG molecules required for lysis. The antibody and complement, however, have to be bound to the same target cell. Bystander complement-coated erythrocytes, present in the same reaction mixture with IgG-coated targets, are not lysed. Blocking of AMCC is effected only by antigen, either soluble or in immune complexes prepared in antigen excess. Antigen competes at the level of the target cell. Blocking at the level of the effector cell, by use of immune complexes prepared at equivalence or in antibody excess, is difficult to achieve. The large number of cells with Fc receptors contained in mouse spleens may explain this finding. Arming of effector cells by passive binding of immune complexes is poorly effective as a means of obtaining lysis of the target cells. In all situations, the outcome of the reaction is determined by the presence of free antibody-combining sites, alone, or in immune complexes, that are able to combine with the target cell membrane antigen. The requirements for lysis are rather stringent.