Transplant Center Policy #228

Desensitization Protocol for Kidney Transplant Candidates Receiving a Deceased Donor Transplant

I. POLICY STATEMENT

Sensitization against HLA antigens limits access to kidney transplantation. Approximately 30% of all kidney transplant candidates active on the wait list are sensitized against Class I and Class II antigens, and it is estimated that 600-1200 sensitized kidney transplant candidates are wait-listed every year. For these patients, median waiting time is substantially longer than for those patients who are not sensitized, and many of these patients will die without having received a kidney transplant.

A protocol consisting of high dose intravenous gammaglobulin (IVIG) with or without rituximab has been shown to improve transplant rates in highly sensitized kidney transplant recipients of a deceased donor transplant, while avoiding hyperacute rejection. Although this protocol does not abrogate the risk of T-cell or antibody-mediated rejection, rejection episodes are responsive to therapy, and early graft survival at 1-year is comparable to that of non-sensitized recipients of an immunologically compatible kidney transplant.

At the University of Transplant Program, the deceased donor desensitization protocol consists of high dose IVIG for 4 consecutive months with 2 additional doses on month 9 and 12. Two consecutive doses of rituximab are administered on months 1 and 2.

The use of B- or plasma cell depletion or complement system blockade will be considered in individual patients.

II. PURPOSE

Desensitization of highly sensitized kidney transplant recipients active on the deceased donor list who do not have a living donor.

III. DEFINITIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ABW</td>
<td>Actual body weight</td>
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<tr>
<td>ATG</td>
<td>Rabbit anti-thymocyte globulin (Thymoglobulin®)</td>
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<tr>
<td>DSA</td>
<td>Donor specific antibody</td>
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<tr>
<td>FFP</td>
<td>Fresh frozen plasma</td>
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<td>FXM</td>
<td>Flow cytometry crossmatch</td>
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<td>IBW</td>
<td>Ideal body weight</td>
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<tr>
<td>IVIG</td>
<td>Intravenous gammaglobulin</td>
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<tr>
<td>MCS</td>
<td>Median Channel Shift</td>
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<tr>
<td>MFI</td>
<td>Mean fluorescence intensity</td>
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<td>PRA</td>
<td>Panel reactive antibody</td>
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IV. STANDARDS

A. Eligibility Criteria

1. Any patient with PRA greater than 50% for ≥3 consecutive tests with waiting time greater than 5 years.

2. Insurance approval of protocol reimbursement.

B. Pre-Transplantation Treatment Phase

1. High dose IVIG and rituximab protocol:
   a. Sucrose-free, isosmolar IVIG preparation 2 g/kg every month for 6 months.
      i. For patients ≤ 100 kg, dose IVIG based on actual body weight.
      ii. For patients > 100 kg, dose IVIG based on adjusted body weight [= IBW + 0.4*(ABW-IBW)].
      iii. Maximal dose of IVIG in all patients = 140 g.
   b. If transplant has not occurred by month 6, two additional doses will be administered on month 9 and 12.
   c. Rituximab 1000 mg will be administered monthly for 2 months.
      i. If rituximab and IVIG are given on the same day, administer rituximab first followed by IVIG.
      ii. In accordance with Chemotherapy Policy 07-01-010, rituximab must be prescribed by authorized chemotherapy-certified prescribers. Their designee may place rituximab orders in but co-signature/verification by an authorized chemotherapy-
certified prescriber is required to complete the ordering process. Without co-signature/verification by an authorized chemotherapy-certified prescriber, pharmacy will not release the order or dispense rituximab. See Exhibit A.

d. Patients on hemodialysis will be dialyzed in the inpatient hemodialysis unit.
e. The transplant coordinator in charge of the desensitization program will contact the nephrology fellow in the transplant rotation who will enter dialysis orders into the electronic ordering system.
f. Once a compatible donor is identified (refer to Table 1), all patients will undergo plasmapheresis followed by low-dose IVIG protocol immediately before transplantation as follows:
   i. One-volume plasma exchange with fresh frozen plasma replacement.
   ii. Sucrose-free, isosmolar IVIG preparation 100 mg/kg after plasmapheresis.
   iii. When necessary, IVIG can be administered during hemodialysis to avoid delays.

2. Additional therapy
   a. Additional doses of rituximab 1000 mg IV q month will be considered in patients refractory to the standard protocol.
   b. Bortezomib (for desensitization) and eculizumab (for induction) treatment will be considered in individual patients or on the basis of a study protocol.

3. Pre-transplant HLA specificity and PRA testing during desensitization procedure:
   a. Single antigen bead testing will be ordered before the first dose of IVIG as a baseline. Five dilutions will be performed in this initial sample (1:1, 1:4, 1:16, 1:64, 1:128). Every antibody with a titer higher than 1:64 will be listed as unacceptable.
   b. After the first dose of IVIG HLA specificity and PRA will be monitored after 2 weeks and 4 weeks, then once a month according to the HLA Laboratory Protocol.
   c. Reporting of unacceptable antigens will be modified according to changes in HLA specificity strength resulting from treatment, and in accordance with the HLA Laboratory standard of procedures (Tables 1 and 2).

4. Cell flow cytometry crossmatch (FXM)
   a. All patients will undergo cell-based flow cytometry* as per the Transplant Program protocol prior to transplantation
   b. Interpretation of FXM* results will take into account the MFI values of DSA (Tables 1 and 2).

   *Please Note: Patients under rituximab treatment will likely show a channel shift increase in the B cell flow crossmatch. Rituximab (anti-CD20) in the patient’s sera will interfere with the reagents used in the reaction. The interference can be decreased with the pronase treatment of the cells, but the level of interference will be related with the concentration of rituximab in circulation.

C. Intraoperative Treatment Phase

1. Methylprednisolone 500 mg IV bolus, and

2. Rabbit anti-thymocyte globulin (ATG, Thymoglobulin®) according to protocol.

D. Post-Transplantation Phase

1. ATG according to the induction protocol.
   a. On plasmapheresis days, ATG must be administered after plasmapheresis.
   b. On days in which plasmapheresis is not being performed, ATG can be administered according to 5C Unit protocol.

2. Standard immunosuppression:
   a. Standard steroid taper.
   b. Tacrolimus 0.075 mg/Kg PO q 12 hrs and adjusted to achieve goal level of 10-12 ng/mL. Tacrolimus will be started immediately post-transplant regardless of the serum creatinine level.
   c. Mycophenolate mofetil 1000 mg PO BID.

3. PP/low-dose IVIG:
   a. Every other day starting on post-operative day 2.
   b. Number of PP/IVIG treatment is determined by the DSA strength at time of transplant (see Table 3).
c. In patients requiring a biopsy or any other invasive procedure ½ FFP will be used as replacement fluid.

4. Monitoring of DSA:
   a. DSA measured by single antigen bead Luminex flow cytometry will be performed before discharge.
      i. Additional treatment will be determined on the basis of this test and 7-10 post-transplant protocol biopsy (see below).
   b. DSA measured by single antigen bead Luminex flow cytometry will be performed any time that an unexplained 25% increase in serum creatinine levels occurs.
   c. Protocol DSA testing (i.e., patients without transplant dysfunction) will be performed at the time of protocol biopsies.

5. Biopsy schedule:
   a. Indication biopsies will be performed at any time of allograft dysfunction as defined as an unexplained 25% increase in serum creatinine levels.
   b. All desensitized patients will undergo a post-perfusion biopsy, and a protocol biopsy at day 7-10 post-transplant.
   c. All desensitized patients will undergo protocol biopsies at post-transplant months 3, 6 and 12 according to the protocol biopsy schedule.
   d. Patients with T-cell or antibody-mediated rejection in surveillance biopsies will be treated according to protocol.

V. EXHIBITS

A. Nursing Tasks in Desensitization for Recipients of Deceased Donor Kidneys

B. Table 1. Criteria Used for Listing of HLA Unacceptable Antigens In UNET and for FXM Interpretation for Transplantation of Primary Recipients Undergoing DDTx Desensitization

<table>
<thead>
<tr>
<th>HLA Loci</th>
<th>Cutoff of Anti-HLA antibodies MFI values§ used for Listing Unacceptable Antigens In UNET for 1ˢᵗ Dx Recipients Undergoing DD Desensitization</th>
<th>Cutoff of DSA MFI values§ and FXM MCS used for Compatibility Assessment in Primary Tx Recipients Undergoing DD Desensitization</th>
</tr>
</thead>
</table>
| A⁺, B⁺, Cw⁺ | -Before desensitization: MFI >3000  
-4-6 months after Desensitization: Every antibody that fall under the cutoff of MFI>3000 should be removed from the Unacceptable Antigen list. | -Single DSA or additive values of multiple DSA  
-MFI <4000; MCS <200* |
| DR¹ and DQB¹ | -Before desensitization: MFI >3,000  
-4-6 months after Desensitization: Every antibody that fall under the cutoff of MFI>3000 should be removed from the Unacceptable Antigen list. | -Single DSA or additive values of multiple DSA  
-MFI <4000; MCS <200*  
-A crossmatch alert will be posted if the patient has antibodies to a specific DQα/DQβ chain combination. With the Flow Crossmatch DR and DQB1 typing from GOLM, in adition the race of the donor will be requested to GOLM. With all this information and HLA frequency data we may be able to accept the right organ. This may not work for every case. - |
| DPA/DPB | No listing in UNET | -MCS <200*  
-Donor DP typing is usually unknown |

¹Allele specific antibodies will not be listed in UNET even for MFI values>3000.
²DQα/DQβ chain specific antibodies will not be listed in UNET even for MFI values>3000.
Antibody titration may be necessary to better assess the strength of antibody reactivity. MFI values of DSA must be <2000 at 1:4 dilution of the patient's serum prior to Tx and after desensitization treatment.

*Rituximab may increase B cell MCS.

C. Table 2. Reporting of Unacceptable Antigens and Criteria for Transplantation in Re-Tx Recipients Undergoing DDTx Desensitization

<table>
<thead>
<tr>
<th>Loci</th>
<th>Criteria For Reporting Of Unacceptable Antigens In Re-Tx Recipients Undergoing DD Desensitization</th>
<th>Antibody strength Criteria for Transplantation for Primary Tx Recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>A and B</td>
<td>MFI &gt;3000</td>
<td>MFI &lt;3,000; MCS &lt;150</td>
</tr>
<tr>
<td>Cw</td>
<td>MFI &gt;3000</td>
<td>MFI &lt;3,000; MCS &lt;150</td>
</tr>
<tr>
<td>DR</td>
<td>MFI &gt;3,000</td>
<td>MFI &lt;3,000; MCS &lt;150</td>
</tr>
<tr>
<td>DPA/DPB</td>
<td>MCS 200*</td>
<td>MCS &lt;150*</td>
</tr>
<tr>
<td>DQA/DQB</td>
<td>MCS 200*</td>
<td>MCS &lt;150*</td>
</tr>
</tbody>
</table>

*Rituximab may increase B cell MCS.

D. Table 3. Post-Transplant Protocol After DDTx Desensitization

<table>
<thead>
<tr>
<th>DSA MFI</th>
<th>Post-Tx IVIG</th>
<th>Pre/Post Tx pheresis</th>
<th>Induction</th>
<th>Post-Tx immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3000</td>
<td>100 mg/kg after each pheresis</td>
<td>1/1-6</td>
<td>ATG</td>
<td>Tacro + MMF + steroids Tacro level = 10-12 ng/mL</td>
</tr>
</tbody>
</table>

VI. REFERENCES