**Transplant Center Policy #233**

**Living Donor Kidney Transplant Desensitization Protocol**

**I. POLICY STATEMENT**

Sensitization against HLA antigens is an immunological barrier to kidney transplantation. Approximately 30% of all kidney transplant candidates active on the transplant list are sensitized against Class I and Class II antigens. Of these, approximately 4000 will have a positive crossmatch against available deceased or living donors.

To overcome antibody barriers to transplantation, several protocols have been implemented that lower donor specific antibody levels, avoid hyperacute rejection, and reduce the incidence of both T-cell and antibody-mediated rejection in sensitized patients. These protocols consist of permutations of plasma exchange, high or low dose intravenous gammaglobulin (IVIG) with or without B-cell depletional therapy. Post-transplant treatment includes continuation of plasma exchange and/or IVIG with frequency determined by the strength of the antibody barrier.

At the University of [Transplant Program], patients identified as having HLA antibody barriers against their living donor are offered enrollment in the Paired Kidney Exchange Program as the optimal choice of transplant enabling intervention. In patients refusing paired kidney exchange or unable to find a compatible match after 6 months of paired matching, living donor desensitization therapy would be considered and offered when appropriate. Living donor desensitization will also be used to enable transplantation between paired kidney exchange matches with HLA antibody-based incompatibilities.

At the University of [Transplant Program], the living donor desensitization protocol consists of plasma exchange followed by low-dose IVIG before and after transplantation. The use of B- or plasma cell depletion or complement system blockade will be considered in individual patients.

**II. PURPOSE**

The purpose of this protocol is to provide general guidelines for desensitization and transplantation of kidney transplant candidates with donor specific antibodies against their living donor.

**III. DEFINITIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ABW</td>
<td>Actual body weight</td>
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<td>DSA</td>
<td>Donor specific antibody</td>
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<td>FFP</td>
<td>Fresh frozen plasma</td>
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<td>FXM</td>
<td>Flow crossmatch</td>
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<td>IBW</td>
<td>Ideal body weight</td>
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<td>IVIG</td>
<td>Intravenous immune globulin</td>
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<td>MCS</td>
<td>Mean channel shift</td>
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<td>MFI</td>
<td>Mean fluorescence intensity</td>
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<tr>
<td>PP</td>
<td>Plasma exchange or plasmapheresis</td>
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<td>STR</td>
<td>Steroids</td>
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<td>Tacro</td>
<td>Tacrolimus</td>
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</table>

**IV. STANDARDS**

**A. Eligibility Criteria**

1. Any primary or multiple kidney transplant candidate with donor specific antibodies (DSA) against his or her only living donor and antibody strength as defined below is considered eligible.
2. Insurance approval of protocol reimbursement.

**B. Pre-Transplantation Treatment Phase**

1. Maintenance immunosuppression: Starting on the first day of desensitization
   a) Tacrolimus 0.03 mg/kg PO q 12 hrs (level=10-12 ng/mL)
   b) Mycophenolate mofetil 500 mg PO BID
2. Plasmapheresis and low-dose IVIG protocol:
   a) One-volume plasma exchange with 5% albumin replacement every other day until completing the planned number of treatments.
   b) Fresh frozen plasma replacement will be used during the last session preceding transplantation.
c) Plasmapheresis will be performed three times per week during business days as an outpatient procedure.
d) Stop ACE or Angiotensin-II inhibitors before pheresis.
e) Can use calcium-channel blockers for blood pressure control if appropriate.
f) Sucrose-free, isosmolar IVIG preparation 100 mg/kg after pheresis treatments #1-7, and during hemodialysis.
g) Sucrose-free, isosmolar IVIG preparation 500 mg/kg after pheresis treatment #8 or final planned exchange (if more than 8 treatments are deemed necessary), and during hemodialysis.
h) IVIG dosing calculation:
   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
i) Patients on hemodialysis will be dialyzed in the inpatient hemodialysis unit.
j) 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.

3. Additional Therapy:
   a) Treatment with rituximab 1000 mg will be considered in patients refractory to the standard protocol defined above.
   **Please note:** 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.
   b) Bortezomib (for desensitization) and eculizumab (for induction) treatment will also be considered in individual patients or on the basis of a study protocol.

4. Pre-transplant DSA testing during desensitization procedure:
   a) A flow crossmatch will be performed in order to correlate with solid phase DSA testing. This will allow as detecting any lack of correlation due to any allele specific DSA without representation in the single antigen panel, or DSA against a specific DQ alpha/beta combination. The flow crossmatch will be performed before any desensitization treatment to avoid drug interferences with the reaction.
   b) Single antigen bead testing will be ordered before the first pheresis as a baseline.
   c) A baseline level will not be necessary if DSA strength testing has been performed within 2 weeks before the initiation of desensitization.
   d) DSA testing will be performed at the middle and before the last planned pheresis treatment.
   e) A DSA strengths deemed appropriate for transplantation are defined in Table 1.

C. Intraoperative Treatment Phase
   1. Methylprednisolone 500 mg IV bolus, and
   2. Rabbit anti-thymocyte globulin (ATG, Thymoglobulin®) according to the induction protocol, initiated before reperfusion of renal allograft.

D. Post-Transplantation Phase: Treatment Protocol
   1. ATG according to the induction protocol.
      a) On pheresis days, ATG must be administered after pheresis.
      b) On days in which pheresis 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) Mycohenolate mofetil 1000 mg PO BID.
3. Plasmapheresis and low-dose IVIG:
   a) Every other day starting on post-operative day 2.
   b) Number of pheresis/IVIG treatments is determined by the initial DSA strength (see Table 2).
   c) In patients requiring a biopsy or any other invasive procedure

4. Monitoring of DSA:
   a) DSA measured by single antigen bead Luminex flow cytometry will be performed before the last
      planned pheresis session.
   b) DSA measure by single antigen bead will be performed with 7-10 day protocol biopsy and 30 days post-
      transplant.
   c) DSA measured by single antigen bead Luminex flow cytometry will be performed any time that an
      unexplained 25% increase in serum creatinine levels occurs.
   d) 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.

V. EXHIBITS

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

B. Table 1. Antibody Strength Criteria Used For Living Donor Selection for Recipients Undergoing Desensitization

<table>
<thead>
<tr>
<th>HLA Loci</th>
<th>Cutoff of Anti-HLA DSA antibodies: MFI values§ used for Living Donor selection</th>
<th>Post treatment DSA MFI target values§ and FXM MCS used for transplant Recipients Undergoing Desensitization with a Living Donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>A, B, Cw</td>
<td>-Before desensitization: MFI: 3000-6000</td>
<td>-Single DSA or additive values of multiple DSA -MFI &lt;2000; MCS &lt;150*</td>
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<tr>
<td>DR, DQ, DP</td>
<td>-Before desensitization: MFI: 3000-6000</td>
<td>-Single DSA or additive values of multiple DSA -MFI &lt;2000; MCS &lt;150*</td>
</tr>
</tbody>
</table>

§Antibody titration may be necessary to better assess the strength of antibody reactivity. MFI values of DSA must be <2000 or titrate 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. Desensitization Protocol Overview

<table>
<thead>
<tr>
<th>DSA MFI (Loci A, B, DR)</th>
<th>IVIG schedule</th>
<th>Pre/Post Tx Pheresis</th>
<th>Pre-Tx immunosuppression</th>
<th>Induction</th>
<th>Post-Tx immunosuppression</th>
</tr>
</thead>
</table>
| 2000-3000               | 100 mg/kg after each pheresis | 2/0 Last Pre-Tx PP with ½ FFP | Tacro + MMF 500 mg PO BID on day -15
Tacro level = 10-12 ng/mL | ATG | Tacro + MMF 1000 mg PO BID+ STR
Tacro level = 10-12 ng/mL |
| >3000-6000              | 100 mg/kg after each pheresis | 4-6/2-4 Last Pre-Tx PP with ½ FFP | Tacro+ MMF 500 mg PO BID on day -15
Tacro level = 10-12 ng/mL | ATG | Tacro+MMF 1000 mg PO BID+ STR
Tacro level = 10-12 ng/mL |

VI. REFERENCES