

Therapeutic Plasma Exchange in Renal Transplantation: Mayo Clinic Approach

Jeffrey L Winters, M.D.
Division of Transfusion Medicine
Mayo Clinic
Rochester MN



DISCLOSURE

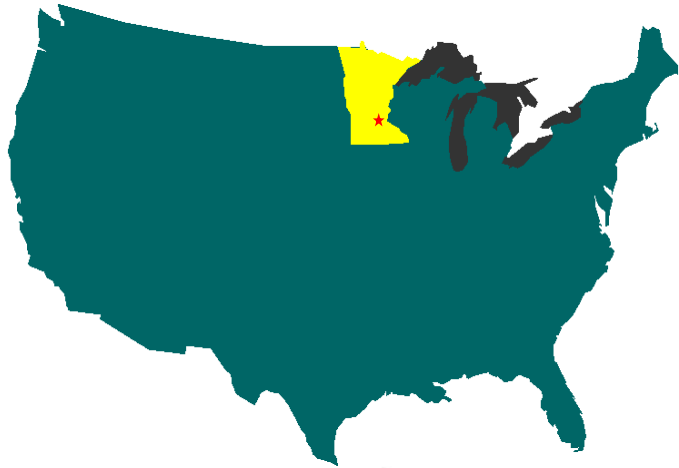
Relevant Financial Relationship(s)

NONE

Off Label Usage

**Rituximab, eculizumab, and bortezomib
for renal transplant conditioning and
treatment of antibody mediated
rejection**

Mayo Clinic Rochester Minnesota



An integrated medical center consisting of the Mayo Clinic, Saint Marys Hospital, and Rochester Methodist Hospital

- **1.4 million outpatient visits annually**
- **48,218 surgical cases annually**
- **1,714 physicians**
- **24,591 allied health staff**
- **1,906 hospital beds**
- **99 operating rooms**



Therapeutic Apheresis



- First procedure performed January 1974
- Procedures performed in the Gonda building
 - 20 RN FTE
 - 15 bed unit
 - Instrumentation:
 - 9 Amicus
 - 7 COBE Spectra
 - 2 UVAR-XTS
 - 1 CellEx
 - 2 Liposorber MA-03
 - 3,012 procedures in 2010
 - 1,492 Plasma exchanges
 - 915 HPC collections
 - 382 Photopheresis procedures
 - 175 LDL apheresis procedures
 - 67 Granulocyte collections
 - 24 Therapeutic T-Cell collections
 - 10 Leukocytapheresis procedures
 - 10 Thrombocytapheresis procedures

Renal Transplant Program

- **First ABO incompatible renal transplant performed 1999**
- **First crossmatch incompatible transplant performed 2000**
- **From September 1999 to May 2011 there have been 2,766 renal transplants. Of these:**
 - **137 (5%) CDC crossmatch incompatible**
 - **113 (4%) flow cytometric crossmatch incompatible**
 - **89 (3%) ABO incompatible using non-A2 kidneys**
 - **12 (0.4%) ABO incompatible using A2 kidneys**
 - **7 (0.3%) ABO and crossmatch incompatible**



Transplant Immunosuppression

- **Same induction and maintenance therapy for all transplant protocols**
 - **Induction**
 - **Anti-thymocyte globulin**
 - **Maintenance**
 - **Tacrolimus or sirolimus**
 - **Mycophenolate mofetil**
 - **Prednisone**

Plasma Exchange

- **Plasma exchange performed the same for all protocols**
 - **1 plasma volume**
 - **5% albumin as replacement fluid**
 - **3 units FFP added as final portion on days 0, +1, and +2**
 - **Partial heparin/ACD-A as anticoagulant**
 - **ACD-A as anticoagulant on days 0, +1, and +2**
- **Plasma exchange followed by IVIG 100 mg/kg**

Focal Segmental Glomerulosclerosis

- **Background**
 - **Nephrotic syndrome**
 - **Caused by a 150 kD permeability factor**
 - **Cause of 11% of childhood and 5% of adult ESRD**
 - **25 to 50% recurrence following transplant**
 - **90% recurrence if history of previous allograft loss due to recurrence**

Focal Segmental Glomerulosclerosis

- **Role of Plasma Exchange**
 - **Prophylactic – reports of reduced recurrence rates and improved graft survival**
 - **Therapeutic - reports of up to 80% remission of proteinuria with PE and ACEI if started within 48 hours of recurrence**

Focal Segmental Glomerulosclerosis

- **Mayo Clinic Experience**
 - **38 of 1573 patients with unequivocal, non-familial FSGS**
 - **47% with recurrence**
 - **Patient treatment**
 - **7 with prophylactic PE**
 - **7 with therapeutic PE**

Focal Segmental Glomerulosclerosis

- **Mayo Clinic Experience**
 - **Protocols**
 - **Prophylactic**
 - **PE on days -5, -3, -1**
 - **Therapeutic**
 - **PE daily for 3 to 7 days post transplant then 3 times per week for 4 to 12 weeks**
 - **Pediatric patients also received rituximab**
 - **Response monitored with albumin/creatinine ratio and 24 hr urine total protein**

Focal Segmental Glomerulosclerosis

- **Mayo Clinic Experience**
 - **Findings**
 - **Greater risk of recurrence with rapidly progressive FSGS and younger age**
 - **Outcomes**
 - **Prophylactic PE – no apparent reduction in recurrence**
 - **Therapeutic PE – 69% with partial or complete response but 3 graft losses and 3 with persistent proteinuria**
 - **4 patients with sustained remission – all received PE and rituximab and all were pediatric patients**

Focal Segmental Glomerulosclerosis

- **Current Protocol**
 - **Rituximab**
 - **Adults – 325 mg/m² on days 1, 7, 14, and 21 or 1 gm days 0 and 15**
 - **Children – 250 mg/m² on days 1, 7, 14, and 21**
 - **Transplant on day 60**
 - **Ureteral ligation if continued native kidney proteinuria**
 - **PE on days 1 through 4 after transplant**
 - **Proteinuria monitored**
 - **Albumin/Creatinine ratio used immediately post transplant**
 - **24 hour urine protein measurements used**
 - **If no proteinuria, PE discontinued**
 - **Additional PE and rituximab added based upon proteinuria**

ABO Incompatible Renal Transplantation

- **Background**
 - **Annual demand (~100,000) exceeds supply (~15,000) for solid organs**
 - **Majority of those awaiting renal transplantation are blood group O**
 - **In the US, the probability that a pair of individuals will be ABO incompatible is 36%**

ABO Incompatible Renal Transplantation

- **Mayo Clinic Experience**
 - **Initial protocol involved transplantation of A2 kidneys**
 - **Titers of 64 to 256**
 - **No PE performed**
 - **2 of 8 patients developed humoral rejection**
 - **PE was added to achieve a titer of ≤ 8**

ABO Incompatible Renal Transplantation

- **Mayo Clinic Experience**
 - **Initial protocol for non-A2 kidneys involved:**
 - **PE with target titer ≤ 16**
 - **Splenectomy at the time of transplant**
 - **8 patients treated initially**
 - **AMR developed in 28%**
 - **100% 1-year graft survival**

ABO Incompatible Renal Transplantation

- **Mayo Clinic Experience**
 - **Because of occurrence of AMR, protocol modified to reduce titer to ≤ 8**
 - **26 patients treated**
 - **AMR developed in 46%**
 - **All occurred within 14 days**
 - **Reversed by PE in 83% (mean of 3.4 PE)**
 - **Patient survival 92% (Deaths due to MI and CVA)**
 - **Graft survival 85%**

ABO Incompatible Renal Transplantation

- **Mayo Clinic Experience**
 - **Splenectomy associated with increased infection risk**
 - **Studies suggest splenectomy not necessary**
 - **Protocol was further modified:**
 - **Identical pretransplant PE and IVIG**
 - **Rituximab administered prior to conditioning**
 - **PE performed posttransplant days 1 and 3 with additional PE to maintain titer ≤ 8 for the first 14 days**
 - **23 patients with splenectomy vs. 11 patients with modified protocol**
 - **Patient survival equivalent: 96% vs. 91%**
 - **Graft survival equivalent: 87% vs. 82%**
 - **AMR equivalent: 30% vs. 18%**

ABO Incompatible Renal Transplantation

- **Mayo Clinic Experience**
 - **2007 rituximab eliminated from crossmatch incompatible transplant protocol without changes in patient or graft survival or increased AMR**
 - **2010 rituximab eliminated from ABO incompatible protocol**
 - **50% occurrence of AMR has resulted in reinstatement of rituximab prior to starting PE**

ABO Incompatible Renal Transplantation

- **Current Protocol**
 - **Rituximab administered prior to start of PE conditioning**
 - **Number of PE prior to transplant determined by titer**
 - **1 tube change per PE**
 - **PE administered daily until titer ≤ 8 and on days 1 and 3 after transplant**
 - **Additional PE to maintain titer ≤ 8 for the first week and ≤ 16 for the second week**
 - **IVIg 100 mg/kg after each PE**
- **ABO incompatible transplants are on hold in favor of the paired kidney transplant program**

Crossmatch Incompatible Renal Transplantation

- **Background**
 - **One third on the renal transplantation wait list have a PRA >10%**
 - **Only receive 19% of deceased donor transplants**
 - **4,000 patients died in 2005 awaiting renal transplantation**
 - **11.1 patients per day**
 - **Renal transplantation doubles average life expectancy compared to dialysis**

Crossmatch Incompatible Renal Transplantation

- **Mayo Clinic Experience**
 - **Initial protocol treated patients with antihuman globulin complement dependent cytotoxicity (AHG-CDC) crossmatch titer ≤ 16**
 - **Rituximab administered prior to conditioning**
 - **PE performed on days -4, -3, -1, and 0**
 - **Goal to achieve a negative AHG-CDC crossmatch**
 - **Splenectomy performed at the time of transplant**

Crossmatch Incompatible Renal Transplantation

- **Mayo Clinic Experience**
 - **14 patients treated**
 - **No hyperacute rejection**
 - **79% graft survival**
 - **2 lost to vasculopathy and 1 to death**
 - **43% with AMR**
 - **14% clinical**
 - **29% subclinical**
 - **Reversible in all with PE**

Crossmatch Incompatible Renal Transplantation

- **Mayo Clinic Experience**
 - **Based upon findings in ABO incompatible transplants that splenectomy was not needed, two protocols with PE and one with IVIG were compared**
 - **PE, rituximab and splenectomy**
 - **PE, rituximab and posttransplant DSA monitoring**
 - **High dose IVIG**

Crossmatch Incompatible Renal Transplantation

- **Mayo Clinic Experience**
 - **PE performed daily to achieve negative AHG-CDC crossmatch**
 - **PE performed for three days after transplant**
 - **In DSA monitoring protocol, PE if BFXM or TFXM channel shift ≥ 300**

Crossmatch Incompatible Renal Transplantation

- **Mayo Clinic Experience**
 - **High dose IVIG – 13**
 - **38% negative crossmatch**
 - **80% AMR**
 - **PE and splenectomy – 32**
 - **84% negative crossmatch**
 - **37% AMR**
 - **PE and monitoring – 16**
 - **88% negative crossmatch**
 - **29% AMR**

Crossmatch Incompatible Renal Transplantation

- **Mayo Clinic Experience**
 - **AHG-CDC crossmatch replaced with TFXM**
 - **Trigger for desensitization was a channel shift of 300**
 - **Correlates with a positive AHG-CDC**
 - **Examined the importance of antibodies to HLA Class II**
 - **12 transplants with only HLA class II antibodies**
 - **7 with DSA**
 - **5 without DSA**

Crossmatch Incompatible Renal Transplantation

- **Mayo Clinic Experience**
 - **DSA against donor Class II**
 - **57% AMR**
 - **1 patient lost graft due to accelerated transplant glomerulopathy**
 - **No DSA against donor Class II**
 - **0% AMR**
 - **Suggested that DSA to HLA Class II important in AMR**
 - **BFXM incorporated into screening**

Crossmatch Incompatible Renal Transplantation

- **Mayo Clinic Experience**
 - **Examined the ability to predict AMR**
 - **41 patients with TFXM or BFXM channel shift ≥ 300**
 - **PE, rituximab, and DSA monitoring**
 - **29 patients with TFXM and BFXM channel shift < 300**
 - **No conditioning but DSA monitoring**

Crossmatch Incompatible Renal Transplantation

- **Mayo Clinic Experience**
 - **Patients with no AMR**
 - **DSA levels decreased by day 4 and stayed low**
 - **Patients with AMR**
 - **DSA levels increased by day 10**
 - **92% with BFXM \geq 359**
 - **Study also showed:**
 - **Single antigen bead correlated with BFXM**
 - **Creatinine insensitive to AMR**

Crossmatch Incompatible Renal Transplantation

- **Mayo Clinic Experience**
 - **Based upon evidence that rituximab eliminated only naïve B-cells and not memory B-cells or plasma cells, it was eliminated from the protocol on 2007**
 - **No changes in patient or graft survival or increased AMR**

Crossmatch Incompatible Renal Transplantation

- **Current Protocol**
 - **BFXM and TFXM channel shift <300**
 - **No conditioning**
 - **Posttransplant, daily DSA monitoring with PE if increase in DSA**
 - **BFXM or TFXM channel shift ≥ 300**
 - **Daily PE until BFXM and TFXM <300**
 - **Posttransplant, daily DSA monitoring with PE if increase in DSA**

Crossmatch Incompatible Renal Transplantation

- **Mayo Clinic Experience**
 - **Additional important findings**
 - **Baseline DSA level associated with risk of AMR but not TG**
 - **Persistence of DSA posttransplant was not associated with AMR**
 - **AMR associated with earlier onset of TG**
 - **Incompatible transplants have shorter graft survival than compatible transplants due to increased TG**

Antibody Mediated Rejection

- **Treatment**
 - **Daily PE followed by IVIG (100 mg/kg)**
 - **Bolus methyprednisolone**
 - **In refractory cases may also add:**
 - **Rituximab**
 - **Splenectomy**

Future Directions

- **Eculizumab**
 - **Humanized monoclonal antibody that inhibits cleavage of C5**
 - **FDA approved for PNH**
 - **Preliminary report of use in 10 crossmatch incompatible transplants**
 - **5 patients with DSA levels during the first week of transplant similar to those seen with AMR**
 - **No dysfunction and no evidence of abnormalities on biopsy**

Future Directions

- **Bortezomib**
 - **Rituximab, ATG, and IVIG ineffective in depleting plasma cells (PC) in the bone marrow**
 - **Proteasome inhibitor induces apoptosis in PC**
 - **Used to treat multiple myeloma**
 - **In vitro studies demonstrate apoptosis of DSA secreting PC**

Future Directions

- **Bortezomib**
 - **8 patients examined**
 - **Decreased DSA secreting PC in the marrow**
 - **Did not result in a significant decrease in DSA**
 - **5 underwent PE**
 - **Greater DSA decrease than in 8 historic controls with equivalent DSA titers receiving PE alone**
 - **2 underwent transplantation**
 - **12 month follow-up - one with no DSA while one with persistent DSA and C4d positivity**

Future Directions

- **Paired Donation**
 - **A, B, O and crossmatch incompatible donor/recipient pairs agree to participate**
 - **Donors are matched with compatible recipients to form pairs and chains**
 - **Avoids ABO and crossmatch incompatible transplants**

References

- **FSGS**
 - **Hickson LJ et al. Kidney transplantation for primary focal segmental glomerulosclerosis: Outcomes and response to therapy for recurrence. *Transplantation* 2008;87:1232-1239.**
- **ABO incompatible**
 - **Gloor JM et al. ABO-incompatible kidney transplantation using both A2 and non-A2 living donors. *Transplantation* 2003;75:971-977.**
 - **Winters JL et al. Plasma exchange conditioning for ABO-incompatible renal transplantation. *J Clin Apher* 2004;19:79-85.**
 - **Gloor JM et al. A comparison of splenectomy versus intensive posttransplant antidonor blood group antibody monitoring without splenectomy in ABO-incompatible kidney transplantation. *Transplantation* 2005;80:1572-1577.**

References

- **Crossmatch incompatible**
 - **Gloor JM et al. Overcoming a positive crossmatch in living-donor kidney transplantation. *Am J Transplant* 2003;3:1017-1023.**
 - **Gloor JM et al. Persistence of low levels of alloantibody after desensitization in crossmatch-positive living-donor kidney transplantation. *Transplantation* 2004;78:221-227.**
 - **Stegall MD et al. A comparison of plasmapheresis versus high-dose IVIG desensitization in renal allograft recipients with high levels of donor specific antibody. *Am J Transplant* 2006;6:346-351.**
 - **Gloor JM et al. Histologic findings one year after positive crossmatch or ABO blood group incompatible living donor kidney transplantation. *Am J Transplant* 2006;6:1842-1847.**

References

- **Crossmatch incompatible**
 - **Ramos EJ et al. The effect of desensitization protocols on human splenic B-cell populations *in vivo*. *Am J Transplant* 2007;7:402-407.**
 - **Pollinger HS et al. Kidney transplantation in patients with antibodies against donor HLA class II. *Am J Transplant* 2007;7:857-863.**
 - **Burns JM et al. Alloantibody levels and acute humoral rejection early after positive crossmatch kidney transplantation. *Am J Transplant* 2008;8:2684-2694.**
 - **Gloor JM et al. Baseline donor-specific antibody levels and outcomes in positive crossmatch kidney transplantation. *Am J Transplant* 2010;10:582-589.**

References

- **Eculizumab**
 - **Stegall MD et al. Prevention of acute humoral rejection with C5 inhibition. *Am J Transplant* 2009;9(suppl 2):241**
 - **Cornell LD, et al. Prevention of endothelial cell activation with C5 inhibition in positive crossmatch kidney transplants. *Am J Transplant* 2009;9(suppl 2)304.**
- **Bortezomib**
 - **Diwan TS, et al The impact of proteasome inhibition on alloantibody-producing plasma cells in vivo. *Transplantation* 2011;91:536-541.**