Rituximab Treatment for Antibody-Mediated Rejection (AMR) Following Heart and Kidney Transplant

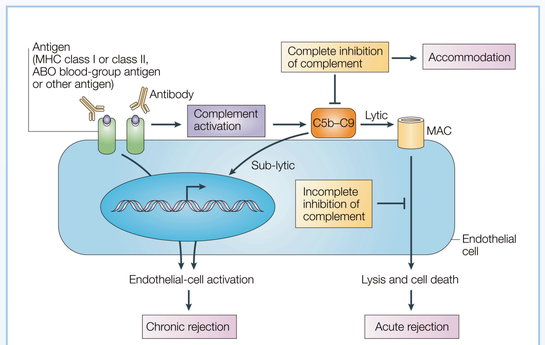
Laura A. Falconieri BA, PharmD; Cheryl A. Abbas PharmD

Department of Pharmacy, Thomas Jefferson University Hospital, Philadelphia, PA

BACKGROUND

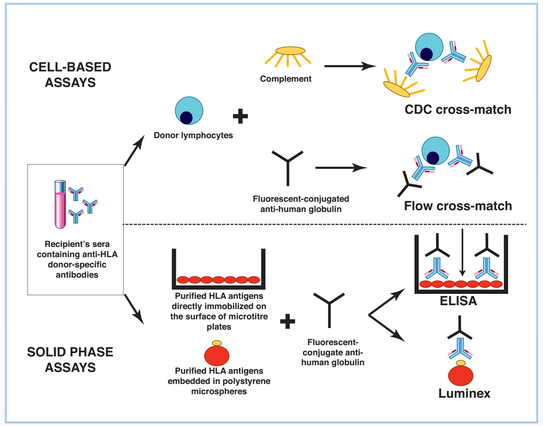
Antibody Mediated Rejection (AMR)[1,2]

- Rejection that occurs due to antibodies against donor-specific antigen (DSA)
  - Antibodies activate complement system
  - Leads to cell death and tissue necrosis
- Risk Factors
  - Pregnancy
  - Blood transfusions
  - Prior transplantation
- Types of AMR
  - Hyperacute
    - Occurs within minutes of graft transplantation causing death of the graft
    - Due to pre-formed antibodies present in high titers
    - Rarely occurs now due to universal cross-matching
  - Acute
    - Occurs within a few days of transplantation causing graft dysfunction
    - Due to pre-formed antibodies or antibodies that develop de novo after transplantation
  - Chronic
    - Occurs during the years following transplantation
    - Due to antibodies that mediate chronic graft injury



Donor Matching[1,2,3]

- Detection of anti-human leukocyte antigen (HLA) antibodies
- Cell-based assays
  - Donor T and B cells are incubated with recipients' sera and complements
  - Donor-specific anti-HLA antibodies will bind to donor cells and initiate the complement cascade resulting in lysis of donor lymphocytes
  - Percentage of lysis is quantified through flow cytometry
- Solid phase assays – Gold standard
  - Latex beads bound with a single HLA are mixed with patient serum
  - Antibodies bind to respective antigen-coated bead
  - Antibodies are tagged with an IgG fluorescent carrier
  - The fluorescence can be detected through flow cytometry
  - Identity and quantity of anti-HLA antibodies is established through intensity of the fluorescence
  - Greater intensity of antibodies in vitro are potentially more cytotoxic in vivo
- Virtual crossmatch through United Network of Organ Sharing database
  - HLA corresponding to high level on anti-HLA antibodies are listed as "avoid"
- Decision about which antibodies to avoid is complicated
  - Highest intensity with fluorescence
  - Ability to bind C1q



Diagnosis of Antibody Mediated Rejection[1,3,4]

- Endomyocardial biopsy is now considered the standard approach to diagnose AMR
  - Routine biopsy surveillance is standard practice as symptoms are often vague
  - Biopsy evaluates:
    - Histologic Findings
      - Activated endothelium
      - Intravascular macrophages
    - Immunologic Findings
      - Complement and HLA deposition
        - C4d and CD68 staining
- Presence of donor-specific antibodies is not required for a diagnosis of AMR
  - May impact aggressiveness of treatment

Pathologic AMR (pAMR) Classification[1,4]

- pAMR0 – Negative for pathologic AMR
- pAMR1 (+I) – Immunopathologic findings positive and histological findings negative
- pAMR1 (+H) – Histological findings positive and immunopathologic findings negative
- pAMR2 – Histological findings and immunopathologic findings are positive
- pAMR3 – Severe AMR with histological findings including interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, and marked edema; associated with profound hemodynamic dysfunction and poor clinical outcomes

		Immunopathology	
		-	+
Histology	-	pAMR0	pAMR1 (I+)
	+	pAMR1 (H+)	pAMR2 pAMR3 (Severe)

TREATMENT

Treatment of AMR[1,5]

- Treatment algorithms vary among institutions
- At this time, there are no consensus recommendations about which agent or combinations of agents should be used as initial treatment
- Treatment options are aimed at reducing the presence of donor-specific antibodies
  - Asymptomatic AMR treatment options
    - Pulse steroids (oral)
    - Intravenous immunoglobulin (IVIG)
    - Targeting higher tacrolimus or cyclosporine levels
  - Acute Symptomatic AMR treatment options
    - IV steroids
    - Antithymocyte globulin
    - Plasmapheresis
    - Rituximab
    - Bortezomib

Rituximab in the Treatment of AMR[6-11]

- Pharmacology
  - Monoclonal antibody that binds to CD20 antigen, found predominantly on pre-B and mature B lymphocytes
  - CD20 regulates early steps in the activation process for cell cycle initiation and differentiation
- Hypothetical Use for AMR
  - Causes a profound depletion of B cells
  - Attenuates the production of antibodies against DSA, leading to decreased rejection
- Evidence for Use
  - Number of case reports and case series have been published regarding the use of rituximab post-heart transplant for the treatment of AMR, most of which showing positive outcomes
    - No prospective studies published at this time
  - Few studies have investigated the use of rituximab in the setting of AMR post kidney transplant

Rituximab for the Treatment of AMR post kidney transplant

Population	Doses of Rituximab	Other Treatments Received	Results
27 patients	1	Thymoglobulin and plasmapheresis	At mean follow-up of 605 days, only 3 kidney grafts were lost
8 patients	4	Plasmapheresis, mycophenolate, tacrolimus, and steroids	81% graft survival at 20 months
26 patients	2	Plasmapheresis and IVIG	90% two-year graft survival for the rituximab group compared to 60% in control group
12 patients	2	High-dose IVIG	91.7% graft survival with rituximab and high dose IVIG compared to 50% for high dose IVIG alone

- Many institutions do include rituximab as an option for the treatment of AMR post heart transplant

PATIENT CASE

Patient History

- 27 year old female
- Past medical history
  - Chronic kidney disease
  - Dilated cardiomyopathy
  - Embryonal vaginal rhabdomyosarcoma with bladder wall involvement – treated with cisplatin and an anthracycline-based chemotherapy at age 3
- In March 2013, the patient's ejection fraction (EF) was 12%, and she required permanent inotropic support with IV dobutamine due to refractory heart failure symptoms
- Patient was listed for heart and kidney transplant in April 2013
- Percentage of PRA prior to transplantation was low

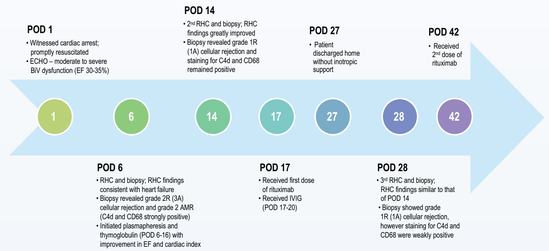
Heart and Kidney Transplant

- Patient received transplant of both organs May 2013
- Overall intra-operative course was uncomplicated
- Patient received basiliximab and methylprednisone intra-operatively
- On post-operative day (POD) 1 the patient experienced a witnessed cardiac arrest and was quickly resuscitated
- Right heart catheterization (RHC) on POD 6 consistent with acute heart failure
- Endomyocardial biopsy on POD 6 revealed:
  - Grade 2R (3A) cellular rejection
  - Grade 2 AMR (C4d and CD68 strongly positive)

Course of Therapy

- Patient received 5 sessions of plasmapheresis alternating with thymoglobulin for 2 doses based upon the absolute lymphocyte count on POD 6-16
- On POD 17, the patient received rituximab 490 mg (375mg/m^2)
- IVIG 500 mg/kg for 4 doses was administered on POD 17-20

Post Operative Clinical Course



CONCLUSION

- Rituximab was effective in treating AMR in this patient
- The growing data on the use of rituximab for AMR may have important implications for the design of treatment regimens in patients with heart and kidney transplants

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DISCLOSURES

- Laura A. Falconieri: Nothing to disclose
- Cheryl A. Abbas: Nothing to disclose