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Elevated De Novo Donor Specific Antibody after Alemtuzumab Induction in Renal Transplant Recipients

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Background

- Alemtuzumab is a humanized monoclonal anti-CD52 antibody used for immunosuppressive induction in renal transplant recipients. Alemtuzumab differs from other induction agents in that it depletes T lymphocytes, B lymphocytes, and NK cells allowing for minimization of maintenance immunosuppression.
- Evidence suggests alemtuzumab induction is associated with development of de novo donor specific antibody (DSA) against human leukocyte antigen (HLA).
- De novo DSA has been associated with antibody-mediated rejection (AMR) and worsened allograft survival.
- A retrospective analysis by Willcombe et al identified a statistically significantly increased odds of AMR with de novo DSA (OR 18.57, p <0.001).
- Todeschini et al compared post-induction B lymphocyte activity of alemtuzumab versus thymoglobulin or basiliximab. Alemtuzumab's early B cell depleting mechanism was correlated to development of de novo DSA. DSA was also associated with negative outcomes in allograft function 1 year post-transplant.
- Recently, the University of Wisconsin (UW) implemented protocol changes to incorporate use of alemtuzumab induction in low immunologic risk (MFI <100) renal transplant recipients in order to facilitate early steroid withdrawal. Thus, it is important to assess the incidence and define the clinical significance of de novo DSA in this population..

Objectives & Purpose

- ***Primary Objective***: define the incidence of de novo DSA in renal transplant recipients who received alemtuzumab induction at the University of Wisconsin Hospital and Clinics from 2010-2015
- ***Secondary Objectives***: conduct descriptive analysis of baseline characteristics, immunosuppression, rejection episodes, and follow-up urine protein and creatinine measurements between patients who developed de novo DSA to those who did not.

Methods

Experimental Design

- Retrospective cohort of adult renal allograft recipients that received a single dose of alemtuzumab (30 mg) transplanted between January 2010 and December 2015. DSA was determined by solid phase single antigen bead testing pre-transplant, then 1 month, 6 month and then yearly post transplant. *(Figure 1)*

Figure 1: Methods

Adult Renal allograft recipients who received one dose of alemtuzumab (30 mg) induction.

Exclusion Criteria:
- Study participant
- Simultaneous organ transplant

Included (n=16)
- ≥ 18 years old
- one dose of alemtuzumab (30 mg) received

- *Data Collected:*
  - *Baseline DSA*
  - *Baseline characteristics*
  - *Discharge immunosuppression*
  - *DSA measurements post-transplant*
  - *Rejection (biopsies) and treatment*
  - *Last follow-up SCr/detectable urine protein*

Results

Table 1. Baseline characteristics

	Total Group (N=16)	No De Novo DSA (N=12)	De Novo DSA (N=4)
Average Age at Transplant, years (SD)	49±11.5	51±13.4	41±10.0
Male (%)	10 (62.5)	6 (50)	4 (100)
White (%)	13 (81.25)	9 (75)	4 (100)
Prior Kidney Transplant (%)	5 (31.25)	4 (33.33)	1 (25)
Prior Blood Transfusion (%)	10 (62.5)	9 (75)	1 (25)
History of Pregnancy (%)	6 (37.5)	6 (50)	N/A
Class I PRA (%)*			
cPRA = 0	11 (68.75)	8 (66.67)	3 (75)
0 < cPRA < 20	1 (6.25)	0	1 (25)
20 ≤ cPRA < 80	3 (18.75)	3 (25)	0
cPRA ≥ 80	0	0	0
Class II PRA (%)*			
cPRA = 0	11 (68.75)	7 (58.33)	4 (100)
0 < cPRA < 20	1 (6.25)	1 (8.33)	0
20 ≤ cPRA < 80	2 (12.5)	2 (16.67)	0
cPRA ≥ 80	1 (6.25)	1 (8.33)	0
History of Malignancy (%)	2 (12.5)	1 (8.33)	1 (25)
Donor Type (%)			
Deceased Brain Donor	7 (43.75)	6 (50)	1 (25)
Deceased Cardiac Donor	4 (25)	3 (25)	2 (50)
Live Donor	5 (31.25)	3 (25)	2 (50)
Cytomegalovirus Status (%)			
Positive	10 (62.5)	9 (75)	1 (25)
Negative	6 (37.5)	3 (25)	3 (75)
Number of Mismatches Class I (%)			
0	1 (6.25)	1 (8.33)	0
2	1 (6.25)	0	1 (25)
4	3 (18.75)	2 (12.5)	1 (25)
5	5 (31.25)	4 (33.33)	1 (25)
6	6 (37.5)	5 (41.67)	1 (25)
Number of Mismatches Class II (%)			
2	3 (18.75)	3 (25)	0
4	6 (37.5)	4 (33.33)	2 (50)
5	6 (35.29)	4 (33.33)	2 (50)
7	1 (6.25)	1 (8.33)	0
Discharge Immunosuppression (%)			
Early Steroid Withdrawal	11 (68.75)	9 (75)	2 (50)
Tacrolimus	15 (93.75)**	11 (91.67)	4 (100)
MMF/Myfortic	16 (100)	12 (100)	4 (100)
Average Cold Time (hours)	12.74	13.47	10.5

baseline cPRA class I and II unknown for one patient
****one patient's tacrolimus held due to DGF***

Results (continued)

Table 2. Follow-up measurements and allograft outcomes

	Total Group (N=16)	No De Novo DSA (N=12)	De Novo DSA (N=4)
Graft Survival (%)	16 (100)	12 (100)	4 (100)
Delayed Graft Function (%)	5 (31.25)	4 (33.33)***	1 (25)
Rejection (%)	5 (31.25)	1 (8.33)	4 (100)
Treated for Rejection (% of those with rejection)	3 (60)	1 (100)	2 (50)
Detectable Urine Protein at Last Follow-up	7 (43.75)	6 (50)	1 (25)
Average Detectable Urine Protein/ Creatinine Ratio	0.16	0.17	0.14
Average Pre-Transplant SCr	7.32	6.85	8.74
Average SCr at Last Follow-up	1.39	1.30	1.63

****One patient had "slow graft function"***

- Primary Outcome:
  - 25% (n=4) of patients developed de novo DSA
- Secondary Outcomes:
  - Average sum MFI of de novo DSA 3600 (312-6493)
  - Average follow up time: 814 days (342-1290 days)
  - Average time to de novo DSA: 387 ±135 days
  - De novo DSA developed in 4 patients following induction with alemtuzumab,
    - 75% (n=3) received a kidney biopsy
      - 100% (n=3) of patients biopsied were found to have rejection
    - 50% (n=2) were treated for rejection
  - Rejection occurred prior to development of de novo DSA in 1 of 4 patients
  - No significant differences in baseline characteristics or follow-up measurements

Conclusion

- In low risk renal transplant recipients, alemtuzumab induction was associated with the development de novo DSA. More studies are needed to characterize the mechanism and risk factors associated with the development of de novo DSA development post kidney transplant and its affect on long term graft kidney allograft survival.

Disclosure

- The authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation