Alemtuzumab Induction vs. Conventional Immunosuppression in Heart Transplant Recipients

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BACKGROUND

- Induction therapy is a strategy for reducing the risk of allograft rejection and immunosuppression-related toxicities in orthotopic heart transplant (OHT) recipients.
- The use of induction in OHT ranges between 62%-83%.[1]
- Alemtuzumab is a humanized rat monoclonal antibody directed against the CD52 antigen on B and T lymphocytes.
- A few small studies in OHT recipients have demonstrated lower rates of rejection, reduced doses of concomitant immunosuppressants, and less steroid use.[2,3]
- The benefits and risks of alemtuzumab induction in OHT recipients at the University of Maryland Medical Center (UMMC) remains uncertain.

PURPOSE

The purpose of this study was to evaluate whether alemtuzumab induction confers a lower risk of rejection compared to standard immunosuppression in OHT recipients with at least one year of follow-up.

OVERVIEW OF STUDY METHODS

Adult OHT recipients at UMMC from January 1, 2010 to March 31, 2016

Inclusion Criteria
- Aged 18-89 years
- Received alemtuzumab induction or conventional immunosuppression

Exclusion Criteria
- Re-transplanted patients
- Multi-organ transplant
- Induction with an agent other than alemtuzumab

Retrospective Chart Review

Alemtuzumab

Conventional immunosuppression

Primary endpoint: freedom from grade ≥ 2 rejection at 12 months after transplantation
Other endpoints: freedom from and time to any rejection, survival, differences in laboratory parameters, concomitant immunosuppression use, infectious complications and biopsy data

STATISTICAL ANALYSIS

- Baseline characteristics and outcomes were compared using ANOVA/t-test, chi-squared/Fisher's exact test or Kaplan-Meier as appropriate.

RESULTS

Characteristic	Control (n=26)	Alemtuzumab (n=26)	P
Recipient age (years)	57.6 (12.8)	55.5 (14.6)	0.524
Male, n (%)	17 (65.4)	22 (84.6)	0.109
Race/ethnicity, n (%)			
White	14 (53.8)	14 (53.8)	0.321
Black	11 (42.3)	8 (30.8)	
Other	1 (6.3)	4 (15.4)	
Heart failure etiology, n (%)			
Ischemic	6 (23.1)	13 (50)	0.044
Nonischemic	20 (76.9)	13 (50)	
Prior VAD, n (%)	15 (57.7)	14 (53.8)	0.780
Hypertension, n (%)	18 (69.2)	14 (53.8)	0.254
Hyperlipidemia, n (%)	12 (46.2)	17 (65.4)	0.163
Diabetes mellitus, n (%)	7 (26.9)	11 (42.3)	0.244
CKD, n (%)	6 (23.1)	12 (46.2)	0.080
CMV Status, n (%)			
Donor CMV+	13 (50.0)	16 (61.5)	0.402
Recipient CMV+	16 (61.5)	15 (57.7)	0.777
High-risk mismatch	5 (19.2)	6 (23.1)	0.734
Serum creatinine (mg/dL)	1.06 (0.3)	1.45 (0.5)	0.029
GFR (mL/min/1.73 m^2)	82.8 (27.5)	64.2 (27.5)	0.018
Proteinuria on urinalysis, n (%)	6 (23.1)	5 (19.2)	0.734
White blood cells (K/mm^3)	10.7 (5.5)	9.7 (5.7)	0.663
Platelets (K/mm^3)	165.1 (66.5)	166.2 (77.6)	0.720
Ischemic time (minutes)	164.8 (69.9)	160.1 (45.2)	0.773
Donor age (years)	31.1 (11.7)	35.9 (12.7)	0.392

CKD chronic kidney disease; GFR glomerular filtration rate; R recipient; VAD ventricular assist device

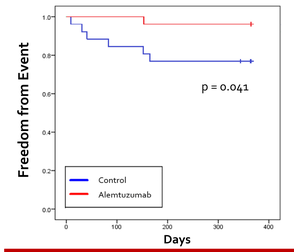
Select Differences at 12 Months

Parameter	Control (n=26)	Alemtuzumab (n=26)	P
Change in SCr from Baseline (mg/dL)	0.4 (0.5)	0.1 (0.4)	0.024
Change in GFR from Baseline (mL/min/1.73 m^2)	-25.6 (28.5)	-9.2 (24.8)	0.032
Platelets (10^3cell/mcL)	198.6 (59.4)	190.0 (57.4)	0.578
WBC (10^3cell/mcL)	5.7 (2.3)	4.8 (1.4)	0.095
ANC (mm^3)	3.8 (2.1)	3.8 (1.9)	0.924
Patients requiring G-CSF	4	9	0.109
Time to GCS-F use, mean (95% CI)	337.9 (306.5-369.2)	311.2 (269.0-353.4)	0.284
PCP Prophylaxis at 6 months	21	8	<0.001
CMV Prophylaxis at 6 months	19	13	0.087

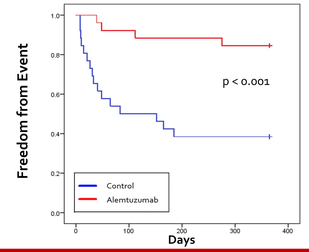
ANC absolute neutrophil count; WBC white blood cells

Rejection-Related Outcomes at 12 Months

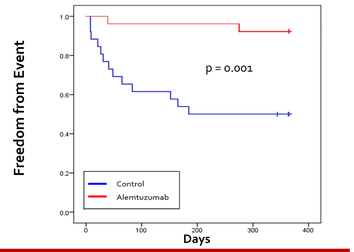
Time to First Grade ≥ 2 Rejection



Time to First Any-Grade Rejection



Time to First Acute Cellular Rejection



Immunosuppression at 12 Months

Tacrolimus

Time	Control (n=26)	Alemtuzumab (n=26)	P-value
Day 7	9.1 (3.8)	4.3 (2.6)	< 0.001
1 month	11.4 (3.3)	7.9 (3.1)	< 0.001
3 months	12.3 (3.9)	8.6 (2.8)	< 0.001
6 months	9.8 (3.5)	8.7 (2.7)	0.268
12 months	12.0 (4.3)	8.8 (5.5)	0.038

Mycophenolate Mofetil

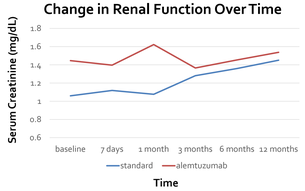
Time	Control (n=26)	Alemtuzumab (n=26)	P-value
Day 7	2000.0 (282.8)	1750 (474.3)	0.026
1 month	2231.0 (452.3)	1516.9 (685.5)	< 0.001
3 months	2019.2 (519.3)	1324.6 (773.4)	0.001
6 months	1942.3 (804.1)	1162.31 (849.0)	0.001
12 months	1692.3 (801.0)	1134.6 (700.8)	0.010

Corticosteroids

Time	Control (n=26)	Alemtuzumab (n=26)	P-value
Cumulative Exposure at 7 days	1958.6 (253.7)	1618.5 (646.7)	0.018
Day 7	26.0 (15.9)	6.9 (6.8)	< 0.001
1 month	16.5 (4.5)	7.3 (4.6)	< 0.001
3 months	12.4 (11.1)	5.4 (3.1)	0.004
6 months	7.2 (4.3)	4.4 (3.3)	0.014
12 months	3.7 (1.8)	2.9 (3.8)	0.310

Other Outcomes at 12 Months

Change in Renal Function Over Time



Outcome	Control (n=26)	Alemtuzumab (n=26)	P
Total Infections (n)	0.69 (1.0)	1.04 (1.5)	0.324
Time to First Infection (days)	292.9 (245.2-340.6)	268.8 (218.8-318.8)	0.422
Readmissions (n)	1.73	1.38	0.427
Patients with ≥ 1 readmission for rejection (n)	8	2	0.035
Time to first readmission (days)	155.3 (95.4-215.2)	191.3 (131.8-250.9)	0.655
Time to first readmission for rejection (days)	283.4 (231.4-335.3)	342.2 (311.5-372.9)	0.038

CONCLUSIONS

- Induction therapy with alemtuzumab appeared to prolong freedom from grade ≥ 2 rejection compared to standard immunosuppression.
- Alemtuzumab was associated with a numeric but not statistically significant reduction in the number of grade ≥ 2 rejections, contrasting with prior studies.[2,3]
- Induction with alemtuzumab appeared to preserve renal function without increasing rates of neutropenia or infectious complications.
  - Renal preservation may be attributable to decreased tacrolimus concentrations in the induction group.
- Similar to earlier studies[2-4], the results suggest that lower mycophenolate doses and tacrolimus goals may be used with alemtuzumab induction.

REFERENCES & DISCLOSURES

None of the investigators involved in this study have any financial or non-financial relationships to disclose. We reference the following publications in this report:

1. Christie JD, Edwards LB, Kucheryavaya AY, et. al. The Registry of the International Society for Heart and Lung Transplantation: Twenty-eighth Adult Lung and Heart-Lung Transplant Report--2011. J Heart Lung Transplant. 2011 Oct;30(10):1104-22.
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4. Pham S.M. Bednar BM, Panos A, et.al. A Randomized Study Using Humanized Monoclonal Antibody Against Cd52 (Campath-1h) and Tacrolimus in Heart Transplant Recipients. J Heart Lung Transplant.2010; 29 (suppl):S50.