Online Data Supplement

Risk Factors for Acute Rejection in the First Year after Lung Transplant: A Multicenter Study

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SUPPLEMENTAL TEXT

METHODS

Cohort

The analysis cohort was drawn from the Clinical Trials in Organ Transplantation (CTOT)-20 (ClinicalTrials.gov NCT02631720) study, a prospective observational study of lung transplant recipients at 5 North American centers. The primary goal of the CTOT-20 study is to examine the clinical and biological risk factors for chronic lung allograft rejection in 800 lung recipients enrolled across these five centers. Centers were selected for participation in CTOT-20 on the basis of transplant volume, specific areas of transplant scientific expertise, and prior productive scientific collaborations. The current analysis, focused on risk factors for acute rejection, represents an early, pre-specified analytic objective of CTOT-20.

General Clinical Management Practices

Duke University: Immunosuppression is induced with methylprednisolone and two doses of basiliximab. Thereafter, maintenance immunosuppression includes prednisone, mycophenolate mofetil and tacrolimus. For patients intolerant of mycophenolate mofetil, azathioprine is substituted. For patients intolerant of tacrolimus, cyclosporine is substituted. Standardized program protocols are followed for calcineurin inhibitor management. For cyclosporine, the goal trough level over the first posttransplant year is 250-300ng/mL, for tacrolimus the goal trough level over the first posttransplant year is 12-14ng/mL. Calcineurin inhibitor trough goals are generally lowered by ~25-35% for recipients of older age or for those who develop chronic kidney disease. Within the first posttransplant year, surveillance bronchoscopies are performed routinely at 1, 3, 6, 9, and 12 months with additional bronchoscopies as clinically indicated. Routine microbiological studies sent from each bronchoscopy include bacterial, fungal, and AFB cultures

in addition to respiratory viral PCR multiplex. Acute rejection or lymphocytic bronchiolitis is treated with methylprednisolone for initial episode and minimal or mild acute rejection. Recurrent or refractory acute rejection or lymphocytic bronchiolitis is treated with antithymocyte globulin or alemtuzumab. Patients treated for acute rejection or lymphocytic bronchiolitis typically are rebiopsied at 4-6 week intervals until two consecutive biopsies demonstrate histological resolution. All patients are monitored serially for the development of anti-human leukocyte antibodies (HLA) including any donor specific antibodies (DSA) at minimum at the time of each posttransplant bronchoscopy. Those patients with a history of DSA have additional screening at each posttranplant clinic visit until antibody resolution. Patients with CMV mismatch (D+/R-) are managed with valganciclovir for the lifetime of the allograft, intermediate risk patients (R+) are managed with valganciclovir for the first posttransplant year, low risk patients (D-/R-) receive three months of acyclovir. All lung recipients receive fungal prophylaxis with fluconazole for the first three months after transplantation. All lung recipients receive pneumocystis prophylaxis with septra or other targeted agent.

University of California Los Angeles: Induction immunosuppression includes methylprednisolone in addition to either antithymocyte globulin 1.5mg/kg given on post operative days 0, 1 and 2 for those under the age of 60 years or two doses of basiliximab given on days 0 and 4 for those aged 60 or greater. Maintenance immunosuppression is with tacrolimus, steroids, and mycophenolate mofetil. For patients intolerant of mycophenolate mofetil, mycophenolic acid or azathioprine is substituted. For patients intolerant of tacrolimus, cyclosporine is substituted. Standardized program protocols are followed for calcineurin inhibitor management. For cyclosporine, the goal trough level over the first posttransplant year is 200-300ng/mL, for tacrolimus the goal trough level over the first posttransplant year is 8-12ng/mL. Within the first posttransplant year,

surveillance bronchoscopies are performed routinely at 1 week (BAL only), and for BAL and biopsy at 1, 3, 6, and 12 months with additional bronchoscopies as clinically indicated. Routine microbiological studies sent from each bronchoscopy include bacterial, fungal, and AFB cultures in addition to respiratory viral PCR multiplex in addition to pneumocystis direct detection, CMV PCR, legionella culture, and mycoplasma PCR. Acute rejection grade A1, which is not accompanied by clinical signs or symptoms is treated with an oral steroid taper. Symptomatic A1 rejection or rejection of grade A2 or higher is treated with IV methylprednisolone. Recurrent or refractory acute rejection is treated with a second pulse of IV methyprednisolone or antithymocyte globulin. Patients treated for acute rejection are typically not rebiopsied unless there are persistent or recurrent signs or symptoms of graft dysfunction. LB that is not accompanied by clinical signs or symptoms is not typically treated with augmented immunosuppression and is not rebiopsied. All patients are monitored serially for the development of anti-human leukocyte antibodies (HLA) including any donor specific antibodies (DSA) at 1, 3, 6, 9 and 12 months posttransplant and annually thereafter. Those patients with a history of DSA have additional screening at each posttranplant clinic visit until antibody resolution. Patients are managed with valganciclovir for the lifetime of the allograft regardless or recipient or donor CMV status. All lung recipients receive fungal prophylaxis with either voriconazole or posaconazole for 6 months in addition to inhaled amphotericin twice weekly for the duration of the postoperative hospitalization. All lung recipients receive pneumocystis prophylaxis with sulfamethoxazole and trimethoprim or other targeted agent.

University of Toronto: Induction immunosuppression over and above methylprednisolone is not routinely used in the absence of a positive crossmatch. If a positive crossmatch is detected antithymocyte globulin for a total of 3-5mg/kg is administered usually beginning on postoperative

day 7. Maintenance immunosuppression is with cyclosporine, prednisone and azathioprine or mycophenolate (if recipient has any panel reactive antibodies at transplant, or if donor-specific antibodies subsequently develop). Cyclosporine is switched to tacrolimus and/or azathioprine is switched to mycophenolate for intolerance, recurrent/refractory acute rejection, or chronic lung allograft dysfunction. Standardized program protocols are followed for calcineurin inhibitor management. For cyclosporine, the goal trough levels over the first posttransplant year are 250-350ng/mL (0-3 months), 250-300ng/mL (3-6 months), 200-250 (6-12 months). For tacrolimus the goal trough levels over the first posttransplant year are 15-20ng/mL (0-6 months), 10-15ng/mL (6-12 months). Calcineurin inhibitor trough goals are generally lowered by ~25-35% for recipients of older age or for those who develop chronic kidney disease. Within the first posttransplant year, surveillance bronchoscopies are performed routinely at 2 weeks, 6 weeks, and at months 3, 6, 9, and 12 with additional bronchoscopies as clinically indicated. Routine microbiological studies sent from each bronchoscopy during the first postoperative year include bacterial, fungal, and AFB cultures in addition to respiratory viral PCR for influenza and respiratory syncytial virus, and galactomannan assay. Acute rejection or lymphocytic bronchiolitis of grade A1 or B1, respectively, which is not accompanied by clinical signs or symptoms is not treated with augmentation of immunosuppression though maintenance immunosuppression will be optimized if possible. Symptomatic grade 1 rejection or rejection of grade 2 or higher is treated with IV methylprednisolone and prednisone augmentation with taper. Recurrent or refractory acute rejection is treated with antithymocyte globulin. Patients treated for acute rejection or lymphocytic bronchiolitis typically are rebiopsied after prednisone taper. All patients are monitored serially for the development of anti-human leukocyte antibodies (HLA) including any donor specific antibodies (DSA) at minimum at the time of each posttransplant bronchoscopy. Patients with CMV

mismatch (D+/R-) are managed with valganciclovir for 9 months posttransplant, intermediate risk patients (R+) are managed with valganciclovir for 6 months posttransplant, low risk patients (D-/R-) receive acyclovir for 3 months posttransplant. Patients with recent pre-transplant or intraoperative respiratory cultures positive for *Aspergillus* or galactomannan receive 3 months of voriconazole. All lung recipients receive pneumocystis prophylaxis with sulfamethoxazole and trimethoprim or other targeted agent.

Johns Hopkins University: Immunosuppression is induced with methylprednisolone and two doses of basiliximab. Thereafter, maintenance immunosuppression includes prednisone, mycophenolate mofetil and tacrolimus. For patients intolerant of mycophenolate mofetil, azathioprine is substituted. For patients intolerant of tacrolimus, cyclosporine is substituted. Standardized program protocols are followed for calcineurin inhibitor management. For cyclosporine, the goal trough levels over the first posttransplant year are 250-300ng/mL (0-3 months), 200-250ng/mL (3-6 months), 100-200 (6-12 months). For tacrolimus the goal trough levels over the first posttransplant year are: 12-15ng/mL (0-3 months), 10-12ng/mL (3-12 months). Calcineurin inhibitor trough goals are generally lowered by ~25-35% for recipients of older age or for those who develop chronic kidney disease. Within the first posttransplant year, surveillance bronchoscopies are performed routinely at 1, 3, 6, 9, and 12 months with additional bronchoscopies as clinically indicated. Routine microbiological studies sent from each bronchoscopy include bacterial, fungal, and AFB cultures in addition to respiratory viral PCR multiplex, direct fluorescence for pneumocystis and CMV early antigen testing. Acute rejection or lymphocytic bronchiolitis of grade A1 or B1, respectively, is treated with an oral steroid taper. More severe grades of rejection or rejection events of any grade associated with a significant spirometric decline are treated with IV methylprednisolone. Recurrent or refractory acute rejection or lymphocytic

bronchiolitis is treated with IV methylprednisolone and with further augmentation individualized per patient.Follow up biopsies are usually conducted 3-6 weeks following detected AR, if safe to do so. All patients are monitored serially for the development of anti-human leukocyte antibodies (HLA) including any donor specific antibodies (DSA) at minimum at of every three months during the first posttransplant year, usually concurrent to bronchoscopy. Patients with CMV mismatch (D+/R-) are managed with valganciclovir for 6 months posttransplant, intermediate risk patients (R+) are managed with valganciclovir for 3 months posttransplant, low risk patients (D-/R-) receive lifelong acyclovir for varicella prophylaxis. Early postoperative fungal prophylaxis in all patients include inhaled amphotericin (for upto 6 weeks or hospital discharge) and oral nystatin, with a third generation azole used in patients with a history of pretransplant *Aspergillus*. All lung recipients receive pneumocystis prophylaxis with septra or other targeted agent.

Cleveland Clinic: Induction immunosuppression over and above methylprednisolone is not routinely used in the absence of a positive crossmatch. In the setting of a positive crossmatch recipients are treated with antithymocyte globulin daily for three to five days in addition to steroids. Maintenance immunosuppression for all recipients includes tacrolimus, steroids, and mycophenolate mofetil. For patients intolerant of mycophenolate mofetil, azathioprine is substituted. For patients intolerant of tacrolimus, cyclosporine is substituted. Standardized program protocols are followed for calcineurin inhibitor management. For cyclosporine, the goal trough level over the first posttransplant year is 250-300ng/mL, for tacrolimus the goal trough level over the first posttransplant year is 12-14ng/mL. Calcineurin inhibitor trough goals are generally lowered by ~25-35% for recipients of older age or for those who develop chronic kidney disease. Within the first posttransplant year, surveillance bronchoscopies are performed routinely at 3 weeks, 6 weeks, 3 months, 6 months, 9 months and 12 months with additional bronchoscopies

as clinically indicated. Routine microbiological studies sent from each bronchoscopy include bacterial, fungal, and AFB cultures in addition to respiratory viral PCR multiplex, legionella PCR, *Pneumocystis Jiroveci* PCR, nocardia culture, aspergillus galactomannan and herpes simplex virus PCR. Acute rejection or lymphocytic bronchiolitis is treated with oral steroid taper for the initial episode of minimal or mild acute rejection. Recurrent or refractory acute rejection or lymphocytic bronchiolitis is treated with escalating doses of intravenous steroids or antithymocyte globulin. Patients treated for acute rejection or lymphocytic bronchiolitis are rebiopsied after 3 weeks to demonstrate histological resolution. All patients are monitored serially for the development of anti-human leukocyte antibodies (HLA) including any donor specific antibodies (DSA) starting on postoperative day 10 and subsequently at the time of each bronchoscopy during the first posttransplant year. Patients with CMV mismatch (D+/R-) and CMV intermediate risk patients (R+) are managed with valganciclovir for at least one year and longer if clinically well tolerated. CMV low risk patients (D-/R-) receive acyclovir for one year. All lung recipients receive fungal prophylaxis with oral itraconazole for 18 months posttransplant in addition to inhaled amphotericin twice weekly until itraconazole levels are therapeutic (serum level >0.4 uq/mL). All lung recipients receive pneumocystis prophylaxis with trimethoprim/sulfamethoxazole or other targeted agent.

SUPPLEMENTAL TABLES

Table E1. Univariable association of enrolling center (considered as a fixed effect) with the outcome of time to first biopsy proven acute rejection (AR) event. Variability in the hazards of AR is observed across the enrolling centers.

Enrolling Center	Hazard Ratio (95% Confidence Interval)	P-value
UCLA vs DUMC	0.40 (0.25-0.64)	<0.01
JHU vs DUMC	0.17 (0.06-0.46)	<0.01
CC vs DUMC	1.12 (0.80-1.57)	0.51
Toronto vs DUMC	0.82 (0.57-1.19)	0.30

JHU = Johns Hopkins University; DUMC= Duke University Medical Center; CC = Cleveland Clinic; UCLA=University of California Los Angeles

Table E2. Clinical characteristics of the study cohort, presented overall and as stratified by enrolling center. Data are presented as count (percentage) or median (1st quartile, 3rd quartile).

Characteristic	Study Cohort (N=400)	UCLA (n=72)	JHU (n=26)	DUMC (n=101)	CC (n=107)	Toronto (n=94)
Baseline Characteristics						
Age At Transplant, years	59.5 (51.0,66.0)	61.0 (54.0,68.0)	60.0 (34.0,63.0)	57.0 (45.0,64.0)	62.0 (56.0,68.0)	58.0 (48.0,64.0)
Sex						
Female	161 (40.3%)	26 (36.1%)	14 (53.8%)	44 (43.6%)	36 (33.6%)	41 (43.6%)
Male	239 (59.8%)	46 (63.9%)	12 (46.2%)	57 (56.4%)	71 (66.4%)	53 (56.4%)
Race						
Black or African American	20 (5.0%)	1 (1.4%)	3 (11.5%)	8 (7.9%)	6 (5.6%)	2 (2.1%)
Other	18 (4.5%)	8 (11.1%)	0 (0.0%)	2 (2.0%)	1 (0.9%)	7 (7.4%)
White	362 (90.5%)	63 (87.5%)	23 (88.5%)	91 (90.1%)	100 (93.5%)	85 (90.4%)
Native Lung Disease						
Obstructive (A)	112 (28.0%)	12 (16.7%)	4 (15.4%)	26 (25.7%)	37 (34.6%)	33 (35.1%)
Vascular/Other (B)	16 (4.0%)	5 (6.9%)	1 (3.8%)	3 (3.0%)	3 (2.8%)	4 (4.3%)
Cystic (C)	55 (13.8%)	5 (6.9%)	9 (34.6%)	21 (20.8%)	5 (4.7%)	15 (16.0%)
Restrictive (D)	217 (54.3%)	50 (69.4%)	12 (46.2%)	51 (50.5%)	62 (57.9%)	42 (44.7%)
LAS at Transplant	38.5 (34.4,46.5)	40.5 (35.9,49.0)	38.9 (36.2, 45.6)	43.3 (36.6, 51.1)	36.9 (34.0, 46.5)	34.0 (33.0, 40.0)
Transplant Characteristics						
Donor Age, years	41.0 (27.5,54.0)	43.0 (27.5,51.0)	35.0 (26.0,43.0)	38.0 (28.0,51.0)	39.0 (25.0,54.0)	50.0 (31.0,61.0)
Donor Sex						
Female	161 (40.3%)	23 (31.9%)	7 (26.9%)	40 (39.6%)	52 (48.6%)	39 (41.5%)
Male	239 (59.8%)	49 (68.1%)	19 (73.1%)	61 (60.4%)	55 (51.4%)	55 (58.5%)
Donor Cause of Death						
Intracranial hemorrhage/blunt injury	227 (56.9%)	52 (72.2%)	15 (57.7%)	63 (62.4%)	62 (57.9%)	35 (37.6%)
Other/Unknown	172 (43.1%)	20 (27.8%)	11 (42.3%)	38 (37.6%)	45 (42.1%)	58 (62.4%)
Recipient/Donor Sex Mismatch						
F/M	60 (15.0%)	13 (18.1%)	11 (42.3%)	17 (16.8%)	9 (8.4%)	10 (10.6%)
M/F	60 (15.0%)	10 (13.9%)	4 (15.4%)	13 (12.9%)	25 (23.4%)	8 (8.5%)
Matched	280 (70.0%)	49 (68.1%)	11 (42.3%)	71 (70.3%)	73 (68.2%)	76 (80.9%)
Ratio Predicted Total Lung Capacity	1.0 (0.9, 1.1)	1.0 (0.9,1.1)	1.2 (1.0,1.4)	1.0 (0.9,1.1)	1.0 (0.9, 1.0)	1.0 (1.0,1.1)
Ischemic Time, hours	6.4 (4.9, 8.1)	4.0 (3.4,4.9)	5.4 (4.7,6.1)	7.2 (6.2,8.0)	5.8 (4.9,7.0)	9.6 (7.8,14.1)
Total HLA Mismatches						
0	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
1	2 (0.5%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (1.1%)
2	9 (2.3%)	3 (4.3%)	0 (0.0%)	2 (2.0%)	2 (1.9%)	2 (2.1%)
3	49 (12.3%)	7 (10.0%)	1 (3.8%)	17 (16.8%)	13 (12.1%)	11 (11.7%)
4	104 (26.1%)	23 (32.9%)	10 (38.5%)	23 (22.8%)	26 (24.3%)	22 (23.4%)
5	144 (36.2%)	24 (34.3%)	11 (42.3%)	34 (33.7%)	43 (40.2%)	32 (34.0%)
6	89 (22.4%)	13 (18.6%)	4 (15.4%)	24 (23.8%)	23 (21.5%)	25 (26.6%)
A Locus Mismatches						
0	22 (5.5%)	5 (7.1%)	1 (3.8%)	6 (5.9%)	7 (6.5%)	3 (3.2%)
1	167 (42.0%)	32 (45.7%)	12 (46.2%)	41 (40.6%)	43 (40.2%)	39 (41.5%)
2	209 (52.5%)	33 (47.1%)	13 (50.0%)	54 (53.5%)	57 (53.3%)	52 (55.3%)
B Locus Mismatches						
0	10 (2.5%)	3 (4.3%)	0 (0.0%)	1 (1.0%)	2 (1.9%)	4 (4.3%)

1	116 (29.1%)	15 (21.4%)	12 (46.2%)	30 (29.7%)	34 (31.8%)	25 (26.6%)
2	272 (68.3%)	52 (74.3%)	14 (53.8%)	70 (69.3%)	71 (66.4%)	65 (69.1%)
DR Locus Mismatches						
0	23 (5.8%)	5 (7.1%)	0 (0.0%)	5 (5.0%)	5 (4.7%)	8 (8.5%)
1	158 (39.7%)	30 (42.9%)	8 (30.8%)	49 (48.5%)	37 (34.6%)	34 (36.2%)
2	217 (54.5%)	35 (50.0%)	18 (69.2%)	47 (46.5%)	65 (60.7%)	52 (55.3%)
Recipient HLA sensitized pretransplant	169 (42.3%)	26 (36.1%)	5 (19.2%)	27 (26.7%)	42 (39.3%)	69 (73.4%)
Transplant Type						
Bilateral	303 (75.8%)	46 (63.9%)	21 (80.8%)	95 (94.1%)	65 (60.7%)	76 (80.9%)
Single	97 (24.3%)	26 (36.1%)	5 (19.2%)	6 (5.9%)	42 (39.3%)	18 (19.1%)
PGD grade 3 within 72 hrs	65 (16.3%)	3 (4.2%)	0 (0.0%)	32 (31.7%)	14 (13.1%)	16 (17.0%)
Induction Immunosuppression						
Basiliximab	178 (44.5%)	48 (66.7%)	26 (100.0%)	99 (98.0%)	0 (0.0%)	5 (5.3%)
Anti thymocyte globulin	25 (6.3%)	23 (31.9%)	0 (0.0%)	0 (0.0%)	2 (1.9%)	0 (0.0%)
None	197 (49.3%)	1 (1.4%)	0 (0.0%)	2 (2.0%)	105 (98.1%)	89 (94.7%)
Maintenance Immunosuppression*						
Tacrolimus	300 (75.0%)	71 (98.6%)	26 (100.0%)	90 (89.1%)	104 (97.2%)	9 (9.6%)
Cyclosporine	100 (25.0%)	1 (1.4%)	0 (0.0%)	11 (10.9%)	3 (2.8%)	85 (90.4%)
Cell-cycle Inhibitor*						
Mycophenolate mofetil	337 (84.3%)	70 (97.2%)	25 (96.2%)	85 (84.2%)	90 (84.1%)	67 (71.3%)
Azathioprine	43 (10.8%)	0 (0.0%)	1 (3.8%)	12 (11.9%)	3 (2.8%)	27 (28.7%)
Other	20 (5.0%)	2 (2.8%)	0 (0.0%)	4 (4.0%)	14 (13.1%)	0 (0.0%)
Azithromycin*	120 (30.0%)	63 (87.5%)	4 (15.4%)	2 (2.0%)	48 (44.9%)	3 (3.2%)
Biopsy Characteristics						
Biopsies/subject	5.0 (4.0,6.0)	3.0 (2.0,4.0)	5.0 (5.0,6.0)	6.0 (5.0,6.0)	6.0 (6.0,7.0)	5.0 (4.0,6.0)
Time to first biopsy, days	30.0 (22.0,38.0)	42.5 (34.0,59.5)	32.0 (29.0, 35.0)	32.0 (28.0,36.0)	22.0 (20.0, 25.0)	27.5 (20.0, 43.0)

*Medication use assessed at time of discharge from the transplant hospitalization.

JHU = Johns Hopkins University; DUMC= Duke University Medical Center; CC = Cleveland Clinic; UCLA=University of California Los Angeles; HLA = human leukocyte antigen; LAS=lung allocation score; PGD=primary graft dysfunction; UNOS=united network for organ sharing

Table E3. Summary of findings with respect to A and B grade rejection on every biopsy over the first posttransplant year of follow up in the study cohort, stratified by enrolling center.

	All Biopsies (N=2026)	**UCLA (n=193)**	**JHU (n=132)**	**DUMC (n=564)**	**CC (n=680)**	**Toronto n=(457)**
A Grade Rejection						
None (A0)	1403 (69.2%)	147 (76.2%)	90 (68.2%)	401 (71.1%)	507 (74.6%)	258 (56.5%)
Minimal (A1)	287 (14.2%)	20 (10.4%)	2 (1.5%)	117 (20.7%)	88 (12.9%)	60 (13.1%)
Mild (A2)	114 (5.6%)	12 (6.2%)	3 (2.3%)	32 (5.7%)	48 (7.1%)	19 (4.2%)
Moderate (A3)	6 (0.3%)	3 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	2 (0.4%)
Severe (A4)	2 (0.1%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ungradable (Ax)	214 (10.6%)	9 (4.7%)	37 (28.0%)	14 (2.5%)	36 (5.3%)	118 (25.8%)
B Grade Rejection*						
None (B0)	1333 (65.8%)	122 (63.2%)	67 (50.8%)	353 (62.7%)	621 (91.3%)	170 (37.2%)
Low-grade (B1R)	66 (3.3%)	25 (13.0%)	1 (0.8%)	7 (1.2%)	22 (3.2%)	11 (2.4%)
High-grade (B2R)	4 (0.2%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	2 (0.3%)	0 (0.0%)
Ungradable (Bx)	622 (30.7%)	44 (22.8%)	64 (48.5%)	203 (36.1%)	35 (5.1%)	276 (60.4%)

*N=1 biopsy was missing a B grade as it was reviewed at an outside hospital

JHU = Johns Hopkins University; DUMC= Duke University Medical Center; CC = Cleveland Clinic; UCLA=University of California Los Angeles