

Review Article

Safety of Kidney Transplantation for Lung Transplant Recipients with End-Stage Renal Failure

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Abstract

Lung transplant recipients may develop profound renal dysfunction due to Stage IV kidney disease following successful lung transplantation (LTX). A comprehensive medical record review was performed for all LTX recipients transplanted from 1988 to 2012 to identify patients who subsequently underwent renal transplantation (RTX) for end-stage renal insufficiency. Sixteen LTX recipients underwent subsequent RTX (6 males, 10 females) at an average of 8.3 years (median 8, range 3-15) following LTX. Forced expiratory volume in 1 second (FEV1) obtained 6-12 months following RTX declined by more than 10% versus stable pre-RTX FEV1 values in only 4 recipients, and no recipients experienced new onset of BOS post-RTX. We conclude that RTX should be considered for those LTX recipients who develop chronic, end-stage renal failure, and that RTX can be performed safely in LTX recipients without significant impact on lung allograft function.

ABBREVIATIONS

BOS: Bronchiolitis Obliterans Syndrome; CKD: Chronic Kidney Disease; CLAD: Chronic Lung Allograft Dysfunction; COPD: Chronic Obstructive Pulmonary Disease; FEV1: Forced Expiratory Volume in One Second; GFR: Glomerular Filtration Rate; HTN: Systemic Hypertension; IPF: Idiopathic Pulmonary Fibrosis; LTX: Lung Transplantation; RTX: Renal Transplantation

INTRODUCTION

Lung transplantation (LTX) is a treatment that is being increasingly used worldwide for end-stage pulmonary disorders such as cystic fibrosis (CF), idiopathic pulmonary fibrosis (IPF), and chronic obstructive pulmonary disease (COPD). Lifelong immunosuppressive medications are required after LTX to prevent acute rejection and chronic lung allograft dysfunction (CLAD) due to bronchiolitis obliterans syndrome (BOS) or other forms of CLAD that may lead to progressive loss of allograft function over time and recipient death [1,2]. Typical immunosuppressive regimens usually include a calcineurin inhibitor (tacrolimus or cyclosporine A), and these agents can have adverse effects on renal tubular function and lead to nephrotoxicity, which is a well-recognized side effect of chronic calcineurin inhibitor administration [3-6]. Additionally, the nephrotoxicity of calcineurin inhibitors can be accentuated by

hemodynamic instability or concomitant use of other drugs that can cause nephrotoxicity and chronic kidney disease (CKD). Other factors such as diabetes mellitus or systemic hypertension (HTN), if present, can also cause or contribute significantly to progressive renal insufficiency.

Up to 65% of lung transplant recipients have been reported to have at least one episode of acute kidney injury within the first weeks following transplant [7,8], and a substantial number of patients can develop CKD that progresses to end-stage kidney disease requiring hemodialysis [8-13]. The risk of developing end-stage kidney disease was found to be especially increased for pediatric patients who received lung transplants versus a significantly lower risk for heart or liver recipients [10]. Mason et al., [12] reported a prevalence of renal failure requiring dialysis of 13% in a lung transplant cohort of 425 patients, and post-transplant chronic kidney injury has been associated with increased mortality after LTX [13-15]. A CKD prevalence in lung transplant recipients of 15.8% at 5 years using a definition of glomerular filtration rate (GFR) <30 ml/min has been reported, and treatment of end-stage renal disease with renal transplantation was associated with significantly improved survival versus dialysis [16]. Risk factors for developing post-LTX renal insufficiency other than an episode of acute kidney injury include renal function impairment at the time of transplant,

higher age, pre-transplant systemic or pulmonary hypertension, and low center transplant volume [4,8,11-13,15].

Transplant centers must determine whether patients who develop CKD that requires renal replacement therapy should be considered as candidates for renal transplantation (RTX), and the number candidates being placed on the kidney transplant waiting list for CKD that develops after successful LTX is gradually increasing [6,17,18]. Given the potential consequences of RTX on the function of the transplanted lung allograft(s) and the risk of calcineurin inhibitor-associated recurrent injury to the transplanted kidney, questions remain regarding the safety of RTX in lung transplant recipients. Therefore, we examined the clinical course of our center's lung transplant recipients who subsequently received kidney transplants for chronic renal failure at our center to evaluate the impact of RTX on lung allograft function when performed following previous LTX.

METHODS

This investigation was approved by the University of Wisconsin Human Subjects Committee (approval number M-2009-1308). A comprehensive medical record review was performed for all lung transplant recipients who underwent LTX at the University of Wisconsin from 1988 to 2012 to evaluate the outcomes of patients who underwent RTX for end-stage renal insufficiency that developed following successful LTX. We sought to determine safety and efficacy of RTX in this patient cohort and to identify significant complications. Sixteen patients who received LTX and subsequently developed renal failure and underwent RTX at our institution were identified (6 males, 10 females). Charts were then analyzed for the primary end-points of pulmonary function over time before and after RTX and renal function following successful RTX. Secondary data that were analyzed included comorbidities, time to RTX, whether BOS was present at the time of RTX, initiation of hemodialysis prior to RTX, and survival and ultimate cause of death (if deceased). Forced expiratory volume in one second (FEV1) was used as the primary measure of lung function and BOS stage, and serum creatinine was used as the primary measure of change in renal function.

RESULTS

Age at time of LTX (Table 1) ranged from 26 to 63 years (mean \pm SEM = 45 ± 3.4 yrs). Indications for LTX were cystic fibrosis (N=6), emphysema (N=9), and radiation fibrosis (N=1). All patients received post-LTX immunosuppression with prednisone, a calcineurin inhibitor (cyclosporine 8, tacrolimus 8), and either azathioprine (N=7) or mycophenolate (N=9).

Time from LTX to RTX ranged from 3 to 15 years (8.3 ± 0.8 yrs). Number of days on the renal transplant waiting list ranged from 0-1278 (mean 385 and median 191). Type of RTX was deceased donor (N=9), living-related (N=4), or living-unrelated (N=3). Conditions associated with renal dysfunction that were present prior to RTX included diabetes mellitus (N=8), HTN (N=12), and polycystic kidney disease (N=1). Ten patients received dialysis prior to RTX.

Forced expiratory volume in 1 second (FEV1) obtained 6-12 months following renal transplant (2.26 ± 0.32 L) changed little versus pre-RTX values (2.37 ± 0.36 L) for the entire group; only 4

of the 16 renal transplant recipients had $>10\%$ (12%, 13%, 15%, and 43%) decline in FEV1 following RTX, and the recipient with the 43% decline in FEV1 had established Stage 2 BOS at the time of RTX yet survived for 3 more years following RTX (Table 1). Additionally, 3 other recipients with Stage 2 BOS and 2 recipients with Stage 1 BOS at the time of RTX had no significant post-RTX decline in FEV1.

No major complications of RTX occurred in any patient with the exception of one patient who had immediate thrombosis of the transplanted kidney that required kidney retransplantation 5 days later. Following RTX all patients received immunosuppression with prednisone, mycophenolate, and a calcineurin inhibitor (cyclosporine in 5, tacrolimus in 11). All recipients survived beyond one year post-RTX (Table 1), and serum creatinine at 1 year post-RTX was 1.30 ± 0.10 mg/dL. None of the patients had delayed recurrence of end-stage renal failure requiring renal replacement therapy or kidney retransplantation.

DISCUSSION

Risk factors for developing CKD following solid organ transplantation include the pre-transplant level of kidney function, and reliance on serum creatinine only as a measure of renal status may overestimate renal function [19]. Other risk factors include advancing age, female gender, diabetes mellitus, systemic hypertension, peri-operative renal insults, requirement for prolonged mechanical ventilation, renal vasoconstriction caused by calcineurin inhibitor exposure, and a pulmonary diagnosis other than COPD [19,20].

Although RTX did not appear to have a significant deleterious effect on lung function for the majority of our patients, lung function also did not improve significantly in any of our RTX recipients. This lack of improvement may be consistent with a prior study that showed that the negative effects of chronic renal failure requiring hemodialysis on lung function are not fully reversed following RTX [21]. The only serious complication that occurred at the time of RTX was an acute renal artery thrombus in one patient that necessitated emergent retransplantation. Adequate renal function was sustained despite post-operative maintenance immunosuppression that included a calcineurin inhibitor in all renal transplant recipients. The cause of death for those patients who expired was not related to their kidney transplant. These findings suggest that RTX can be performed safely in lung transplant recipients and should be considered for those who develop renal failure. This is consistent with previous reports [22-24], although the reports authored by Lonzo et al., [23] and Tarnow et al., [24] focused entirely on recipient and renal allograft survival and did not report whether their lung recipients experienced any significant impact on lung allograft function once recipients had stabilized following RTX. Additionally, although the presence of advanced kidney disease in patients with end-stage lung disease has been considered by most centers to be a contraindication to LTX, reports of successful dual transplantations (simultaneously performed lung and RTX) exist [22,25-27], and further investigation into the risks and benefit of such operations is warranted.

One obvious limitation of our study is the small number reviewed of LTX recipients who underwent RTX (n=16). While

Table 1: Subject data.

Subject #	LTX Indication	LTX Type	Age (at time of LTX) in years	Gender	DM (Pre/Post)	Years to RTX (post-LTX)	Dialysis?	BOS Stage at RTX	Type of RTX (Source)	FEV1 pre-RTX (liters)	FEV1 post-RTX performed 6-12 months post-RTX (liters)	Δ FEV1>10%?	Post-RTX Cr (early) (gm/dl)	Post-RTX Cr (at 1 year) (gm/dl)	Change in Cr (post-RTX recovery to 1 year post-RTX)	Status	Post-RTX survival (years)	Survival post-LTX (years)	Cause of death
1	PF	BIL	26	F	No	5	Yes	0	DD	1.77	2.07	No	1.3	1.6	0.3	D	11	16	Viral infection
2	E	BIL	45	F	No	10	No	0	LR	3.67	3.22	Yes	0.9	1.0	0.1	A	12.5	22.5	NA
3	E	BIL	51	M	Yes	8	Yes	2	LR	2.05	1.17	Yes	0.9	1.2	0.3	D	3	11	Respiratory failure
4	CF	BIL	29	F	Yes	8	Yes	1	LR	2.37	2.67	No	1.0	1.2	0.1	A	11.5	19.5	NA
5	CF	BIL	28	M	Yes	8	Yes	2	DD	2.23	2.33	No	1.5	1.9	0.4	D	3	11	Sepsis
6	E	SLR	55	M	No	7	Yes	0	DD	1.53	1.68	No	1.0	1.7	0.7	D	5	12	Metastatic carcinoma to stomach & liver
7	CF	BIL	40	M	Yes	9	Yes	0	DD	3.29	3.27	No	1.2	1.3	0.1	D	6	15	Bacterial pneumonia
8	E	BIL	42	F	No	10	Yes	0	DD	2.55	2.21	Yes	1.2	1.6	0.4	A	9.5	19.5	NA
9	E	SLL	56	F	No	6	Yes	2	DD	0.91	0.98	No	0.9	0.9	0	D	6.5	12.5	Lymphoproliferative disorder
10	E	SLL	63	F	No	7	No	2	DD	0.93	1.16	No	0.7	0.8	0.1	D	6	13	Lung cancer
11	CF	BIL	38	M	Yes	13	No	0	DD	5.29	5.07	No	1.2	1.4	0.2	A	4	17	NA
12	E	SLL	61	F	Yes	7	Yes	0	LR	0.84	0.79	No	0.6	0.9	0.3	A	3.5	10.5	NA
13	CF	BIL	39	F	Yes	10	No	0	LUR	1.89	1.97	No	0.6	1.45	0.85	A	3	13	NA
14	E	SLL	61	F	No	7	No	1	LUR	0.94	0.89	No	1.3	1.3	0	A	2.7	9.7	NA
15	CF	BIL	30	M	Yes	15	Yes	0	DD	5.18	4.42	Yes	1.2	1.46	0.26	A	1.5	16.5	NA
16	E	BIL	55	F	No	3	No	0	LUR	2.43	2.22	No	1.3	1.33	0.03	A	1	4	NA
Mean \pm SEM	--	--	45 \pm 3.4		--	8.3 \pm 0.8y	--	--	--	2.37 \pm 0.36	2.26 \pm 0.32	--	1.1 \pm 0.1	1.3 \pm 0.1	0.3 \pm 0.1	--	--	--	NA

Abbreviations: A: Alive; BIL: Bilateral Lung Transplant; BOS: Bronchiolitis Obliterans Syndrome; CF: Cystic Fibrosis; Cr: Serum Creatinine; D: Dead; DD: Deceased Donor; DM: Diabetes Mellitus; E: Emphysema; FEV1: Forced Expiratory Volume In One Second; LR: Living-Related; LTX: Lung Transplant LUR: Living-Unrelated; NA: Not Applicable; PF: Pulmonary Fibrosis; RTX: Renal Transplant; SEM: Standard Error Of The Mean; SLL: Left Single Lung Transplant; SLR: Right Single Lung Transplant

calcineurin inhibitor toxicity was the presumed major cause of renal failure in all of the patients in our study, renal pathologic changes consistent with calcineurin inhibitor toxicity were not routinely verified by biopsy or autopsy. Eight of 16 recipients had diabetes mellitus, and many also had systemic hypertension, which could have been independent causes of renal failure rather than merely contributing factors. At least one study that attempted to distinguish renal failure etiologies via biopsy in lung transplant recipients showed that only 35.5% showed predominant features of chronic calcineurin inhibitor nephrotoxicity [28].

As the number of patients who undergo LTX gradually increases, more recipients are likely to develop severe CKD that requires renal replacement therapy, especially when receiving calcineurin inhibitor-based chronic immunosuppression. Given the significant costs, inconvenience, and complications associated with hemodialysis (especially in already immunosuppressed patients), RTX will remain an attractive option and can significantly improve quality of life. Our experience suggests that lung transplant recipients can do very well if RTX is performed for delayed-onset, severe CKD that is unresponsive to medical therapies.

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Author contributions

Drs. McMenomy and Meyer take full responsibility for the integrity of the work as a whole, from inception to published article.

Mehgan Holland contributed to data collection and analysis and manuscript composition

Dr. McMenomy: contributed to the study design, data collection, statistical analysis, data interpretation, and manuscript composition.

Dr. De Oliveira: contributed to the study design, data

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Dr. Maloney: contributed to the study design, data collection, data interpretation, and manuscript composition.

Dr. Cornwell: contributed to the study data collection, data interpretation, and manuscript composition.

Dr. Meyer: conceived of and contributed to the study design, data collection, statistical analysis, data interpretation, and manuscript composition.

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