ORIGINAL ARTICLE

Belatacept for renal rescue in lung transplant patients

Irina Timofte[1], Michael Terrin[2], Erik Barr[2], Pablo Sanchez[3], June Kim[1], Robert Reed[4], Edward Britt[1], Bharath Ravichandran[5], Keshava Rajagopal[6], Bartley Griffith[3], Si Pham[3], Richard N. Pierson III[7] & Aldo Iacono[8]

1 Division of Pulmonary and Critical Care, Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA
2 Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD, USA
3 Division of Cardiac Surgery, Department of Surgery, University of Maryland School of Medicine, Baltimore, MD, USA
4 Division of Pulmonary and Critical Care,Department of Medicine, VA Maryland Health Care System, University of Maryland School of Medicine, Baltimore, MD, USA
5 Department of Pharmacy, University of Maryland School of Medicine, Baltimore, MD, USA
6 Center for Advanced Heart Failure, Department of Cardiothoracic and Vascular Surgery, University of Texas-Huston, TX, USA
7 Division of Cardiac Surgery, Department of Surgery, VA Maryland Health Care System, University of Maryland School of Medicine, Baltimore, MD, USA
8 Departments of Medicine and Surgery, R Adams Cowley Shock Trauma Center, University of Maryland School of Medicine, Baltimore, MD, USA

Key words
belatacept, calcineurin inhibition, immunosuppression, lung transplant, renal failure

Correspondence
Irina Timofte MD, Division of Pulmonary and Critical Care,

SUMMARY

Renal failure causes morbidity and mortality after lung transplantation and is aggravated by exposure to nephrotoxic immunosuppressant (IS) drugs. We report an off-label experience using belatacept for lung transplant recipients with severe renal insufficiency to reduce nephrotoxic IS exposure. We analyzed data retrospectively from a consecutive series of lung transplant patients with renal insufficiency in whom belatacept treatment was initiated between June 2012 and June 2014 at the University of Maryland Medical Center. Eight patients received belatacept because of acute or chronic renal insufficiency (median) GFR 24 (IQR 18–26). Glomerular filtration rate (GFR) remained stable in two patients and increased in five." One patient with established renal and respiratory failure received only the induction dose of belatacept and died 4 months later of respiratory and multisystem organ failure. Calcineurin inhibitor or sirolimus exposure was safely withheld or reduced without moderate or severe acute rejection during ongoing belatacept in the other seven patients. FEV_1 remained stable over the 6-month study interval. Belatacept use appears to permit safe transient reduction in conventional immunosuppressive therapy and was associated with stable or improved renal function in a small retrospective series of lung transplant recipients with acute or chronic renal insufficiency.

Transplant International 2016; 29: 453–463

doi:10.1111/tri.12731

Department of Medicine, University of Maryland School of Medicine, 2nd Floor, 110 S. Paca St., Baltimore, MD, 21201, USA.
Tel.: 410 328 2864;
fax: 443 462 3045;
e-mail: Itimofte@medicine.umaryland.edu

Conflicts of interest
The authors have no significant conflicts of interest with any companies or organization whose products or services may be discussed in this article.

Received: 13 June 2015
Revision requested: 19 August 2015
Accepted: 9 December 2015
Published online: 8 February 2016

Introduction

Renal insufficiency is an important source of morbidity and is associated with increased mortality following lung transplantation [1,2]. Multiple factors contribute to acute and chronic kidney dysfunction in lung transplant recipients, including baseline pretransplantation renal insufficiency, recipient comorbidities such as diabetes and vascular disease, and acute kidney injury during the perioperative period. Exposure to conventional immunosuppressive agents (IS) (e.g., calcineurin inhibitor (CNI) and mammalian target of rapamycin (mTOR) inhibitors) is well recognized as a major contributor to acute and chronic renal insufficiency [3–5]. CNI nephrotoxicity presents in two distinct but overlapping forms acute and chronic renal injury. Acute nephrotoxicity is a dose-dependent, hemodynamically mediated disorder that is usually reversible with reduction in CNI dose. Chronic nephrotoxicity is an insidious lesion, characterized by an irreversible and progressive renal interstitial fibrosis, which may cause important impairment in renal function culminating with end-stage renal disease. While mammalian target of rapamycin (mTOR) inhibitors were initially publicized as renal-sparing, extensive experience in heart, liver, and lung recipients has revealed that mTOR-associated proteinuria, glomerulonephropathy, and nephrotoxicity occur in a significant minority of patients [5]. Rapamycin cause direct tubular and to a lesser degree, glomerular toxicity and may potentiate CNI toxicity. In lung and other extra-renal transplant recipients, renal function typically deteriorates most quickly during the first 6-month post-transplantation when conventional IS tends to be relatively intensive, and with a variable but often inexorable further decline thereafter despite efforts to minimize IS exposure [6,7].

After belatacept was approved in 2011 to replace CNI for chronic CNI-based immunosuppression in kidney transplant recipients, we began to explore its off-label 'compassionate care' use for lung transplant recipients whose acute or chronic renal insufficiency thought to be exacerbated by CNI or mTOR use, and who appeared refractory to our conventional IS dose-reduction strategies. We hypothesized that belatacept might safely permit further reduction in or even temporary withholding of conventional IS exposure, and facilitate improved recovery of renal function.

Here we report our retrospective review of outcomes in eight lung transplant patients who received belatacept in the context of renal insufficiency.

Patients and methods

Patient selection

Eight patients were treated with belatacept at the University of Maryland Medical Center (UMMC) between June 2012 and July 2014, at the discretion of their lung transplant physician on an off-label compassionate use basis.

After receiving IRB approval, we retrospectively reviewed clinical and laboratory data on lung transplant

recipients who were started on belatacept. General demographic and clinical data, including surgical procedures and other postoperative variables, were abstracted from each patient's medical record. Belatacept was initiated in each patient to allow the reduction of CNI exposure in the context of progressive or recurrent acute renal insufficiency, and when alternative approaches (mTOR inhibitor substitution, CNI reduction alone) were either ineffective or were deemed clinically unwise. It was considered clinically unwise to start or resume rapamycin for patients with thrombocytopenia, uncontrolled hypertrigliceremia, or recent major surgery and failure to respond to rapamycin. It was also considered clinically unwise to decease CNI dose for patients unable to tolerate antimetabolites and had a previous history of acute (three patients) or chronic rejection (five patients).

Bronchiolitis obliterans syndrome (BOS) is clinically defined as a sustained pulmonary decline with a reduced FEV_1 (more than 20%) for more than 3 weeks and the exclusion of acute allograft rejection, anastomotic complications or stricture, infection, or other disease affecting pulmonary function.

Glomerular filtration rate (GFR) was estimated using the CKD-EPI (Chronic Kidney Disease-Epidemiology Collaboration) creatinine equation [8].

An infection event is defined as a significant infectious pathogen (bacterial, viral, or fungus) isolated from BAL.

Patients on belatacept were compared with an historical reference group of patients from the investigator's clinical cohort of patients who developed renal insufficiency also following transplant between 1992 and 2007, and who were managed prior to belatacept availability, that is, before 2011 ($n = 66$). Each patient's first peak creatinine above 2.9 mg/dl was treated as their baseline for time of onset of renal insufficiency. A follow-up creatinine value was selected by identifying the value measured at the closest interval to 6 months ($\pm$up to 2 months) after the baseline value. The date of first elevated Cr was considered baseline for reference group.

Clinical management

Immunosuppression protocol

Initial immunosuppression after lung transplant at UMMC was based on conventional triple-drug therapy: CNI (cyclosporine or tacrolimus); mycophenolate mofetil (MMF) or azathioprine; and corticosteroids. With some variability in practice, all UM lung transplant patients were started initially after transplant on tacrolimus with a blood level goal of 10–14 ng/ml; mycophenolate mofetil 1000 mg two times daily or azathioprine 2 mg/kg daily; and prednisone 10 (if alemtuzumab or anti-thymocyte globulin induction therapy was used) or 20 mg/daily (without induction). When a lung recipient developed renal insufficiency (serum creatinine generally above 1.8 mg/dl), as first-line treatment CNI dose was reduced targeting a trough level goal of 4–8, with or without addition of sirolimus; or sirolimus was substituted for CNI. Routine post-transplant infection prophylaxis included trimethoprim–sulfamethoxazole, voriconazole, and valganciclovir.

Before belatacept initiation, three study patients were switched from tacrolimus to oral cyclosporine after developing neurologic toxicity ascribed to tacrolimus. Inhaled CsA is commonly used at our center, and two patients received inhaled cyclosporine after developing CNI-related nephrotoxicity as part of a separate clinical trial (Registration number NCT01650545).

Three patients with progressive renal toxicity were started on rapamycin before belatacept was initiated. Rapamycin was discontinued about 2 weeks before belatacept was started after the development of side effects and/or in association with a major surgical procedure. Events that prompted discontinuation of rapamycin in one patient each were thrombocytopenia, renal failure, and cardiovascular surgery. No case received rapamycin at belatacept initiation. Patient 8 developed renal failure requiring hemodialysis while on rapamycin prompting belatacept initiation. Therefore, rapamycin was stopped 13 days before starting belatacept.

The rejection surveillance protocol at UMMC includes routine bronchoscopy at 1 month and then every 3 months for 1 year. Additional bronchoscopy and biopsy procedures are performed based on patient symptoms or pulmonary function testing (PFT) decline. After belatacept initiation, patients continued to be followed on the standard lung transplant clinical follow-up protocol. Four of eight patients underwent transbronchial biopsies after belatacept. Only one patient (patient #5) was diagnosed and treated for acute low grade (A1B0). Regular chemistry panels (including BUN and creatinine) and therapeutic drug monitoring was generally completed every 1–2 weeks.

Belatacept protocol

The intent of adding belatacept was to reduce CNI exposure associated with either acute or chronic renal dysfunction. When the standard CNI reduction or

mTOR substitution regimen was not tolerated, or if renal insufficiency persisted or worsened, belatacept was added and CNI or mTOR inhibitor trough levels were further reduced either persistently (in three patients who were treated with ongoing belatacept) or transiently during belatacept use. The belatacept dose regimen was as follows: 10 mg/kg at day 0 and 4, again on weeks 2 and 4, and (for chronic treatment patients only) then monthly thereafter. One patient with established renal and respiratory failure received only the two induction doses of belatacept.

The decision to add belatacept was solely at the discretion of the treating clinicians. If patients developed renal insufficiency, belatacept was added to their existing tacrolimus- or cyclosporine-based regimen while CNI or mTOR treatment intensity was temporarily discontinued, or dosing targets were reduced. In the latter circumstance, target blood trough level was generally decreased to 2–6 ng/ml for tacrolimus; 4–6 ng/ml for sirolimus; and 75–100 ng/ml for cyclosporine. During belatacept initiation and for several subsequent months until a stable treatment regimen was re-established, IS and creatinine monitoring frequency was typically intensified.

Clinical variables guiding patient treatment

Recovery of renal function to normal (defined as GFR > 60, Cr < 1.5 mg/dl off renal replacement) or prevention of further decline in renal function (measured by GRF and serum Cr) was the primary outcome variable used to direct belatacept duration and IS management. Secondary variables used to direct specific management decisions included serial FEV_1 measurements; histologic rejection and infection incidence; and change from baseline CNI exposure measured as a percentage from baseline immunosuppression.

Statistics

Data were analyzed using the Wilcoxon rank-sum test. Statistical significance was set at $P < 0.05$ and all tests were two-sided. Data were presented as median (interquartile range) except where otherwise indicated. Box plots demonstrate median, and first and third quartiles of data.

Patients on belatacept were compared with a reference group of historical patients from the investigators clinical cohort who also developed renal insufficiency at similar intervals following transplant between 1992 and 2007. Sixty-six patients were identified with an elevated 'baseline' creatinine value and a recorded 6-month creatinine follow-up. Their FEV1 values at these time points were also recorded. For statistical purposes, in the belatacept cohort and the reference cohort, if a patient was on dialysis or died in the context of severe renal insufficiency, that patient's creatinine value was analyzed as ranking worst. Change in median creatinine and FEV1 by cohort was tested using the Wilcoxon rank-sum test.

The infection rate in belatacept-treated patients was compared with historic controls, calculated as infection events per 30 days of follow-up.

Results

Between April 2008 and August 2013, 132 lung transplant (LT) procedures were performed at UMMC. Since June 2012, eight patients received a median of three doses (2–9) of belatacept, initiated on median postoperative day 585 (139–1414). All eight patients had normal renal function pretransplant (median creatinine 0.9 mg/dl; range 0.6–1.1 mg/dl; GFR > 60). Three patients were receiving renal replacement therapy for acute or acute-on-chronic renal failure at belatacept initiation. Patient characteristics are summarized in Tables 1 and 2.

Renal function and creatinine/GFR

In belatacept-treated patients, without including the deceased patient, median GFR at belatacept initiation [24 ml/min/1.73 m^2 (IQR 18–26)] increased to 28 (20–60) at 1 month, $P = 0.10$; 31 (27–39) at 3 months, $P = 0.02$; and 36 (25–60) at 6 months after belatacept initiation, $P = 0.01$) (Table 3).

There was a trend toward improvement in creatinine values from baseline at the time of belatacept initiation. Two patients on dialysis were successfully weaned off renal replacement therapy, with serum creatinine levels <1.1. Two more patients with creatinine levels >2.0 improved to creatinine levels <2.0. In all three patients with chronic renal insufficiency at belatacept initiation (patients 1–3) and who were maintained on belatacept with reintroduction of low-dose CNI (target trough ~2), renal function stabilized at creatinine levels around 2.0 and GFR > 25. Of the three patients on hemodialysis prior to receiving belatacept, one remained hemodialysis-dependent and died; the other two became dialysis-free between 6 and 13 days after belatacept initiation.

The deceased patient, who received only the induction dose(s) of belatacept, was on hemodialysis prior to receiving belatacept, remained hemodialysis-dependent, and died after 4 months of multisystem organ failure

Table 1. Belatacept patient characteristics

Pt.	Age	Sex	Indication for transplant	Type of transplant	CNI at time of belatacept initiation	Adjuvant immuno suppression at time of belatacept initiation	BOS at time of belatacept initiation	Renal failure preTx	DM preTx	HTN preTx
1	66	F	Pulmonary fibrosis	Single-lung	Tacrolimus	Inhaled cyclosporine	Yes	No	No	Yes
2	72	F	Pulmonary fibrosis	Bilateral-lung	Tacrolimus	Inhaled cyclosporine	Yes	No	No	No
3	57	M	PAP	Bilateral-lung	Tacrolimus		Yes	No	No	No
4	71	M	Pulmonary fibrosis	Single-lung	Tacrolimus	Mycophenolate mofetil	No	No	No	Yes
5	74	F	Pulmonary fibrosis	Single-lung	Cyclosporine	Mycophenolate mofetil	Yes	No	No	No
6	71	F	COPD	Single-lung	Tacrolimus	Mycophenolate mofetil	No	No	No	No
7	74	M	Pulmonary fibrosis	Single-lung	Tacrolimus		Yes	No	Yes	No
8	74	M	Pulmonary fibrosis	Single-lung	Cyclosporine	Mycophenolate mofetil	No	No	No	Yes

Tx: each row represents the demographic and clinical characteristics of each patient who received belatacept treatment. Tx, transplant; M, male; F, female; BOS, bronchiolitis obliterans syndrome; PAP, pulmonary alveolar proteinosis; CNI, calcineurin inhibitor; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension.

Table 2. Belatacept and renal function

Pt.	Belatacept initiation in relation to Tx (POD)	Belatacept dose (mg)	Reason for discontinuation	Renal insufficiency at time of belatacept initiation	Cr at belatacept initiation	GFR at belatacept initiation	Cr at CNI transition	GFR at transition
1	1414	8	Ongoing	Chronic	2	25	N/A	N/A
2	987	9	Ongoing	Chronic	1.92	26	N/A	N/A
3	2176	8	Ongoing	Chronic	3.1	21	N/A	N/A
4	405	3	Renal recovery	Acute	4.3	14	1.3	>60
5	347	2	Renal recovery	Chronic	1.82	24	2.3	20
6	139	2	Renal recovery	Acute	CVVH	CVVH	0.7	>60
7	761	2	Transfer	Chronic	HD	HD	HD	HD
8	327	3	Renal recovery	Acute	HD	HD	1.24	57

Tx, transplant; POD, postoperative day; HD, hemodialysis; CVVH, continuous veno-venous hemofiltration; Belatacept initiation in relation to Tx, number of days after transplant when belatacept was started; Cr, creatinine; N/A, not applicable because patient continued to receive belatacept for more than 6 months. Cr at CNI transition, creatinine when the patient restarted CNI after receiving belatacept; GFR at transition, GFR when the patient restarted CNI after receiving belatacept.

associated with persistent pulmonary atypical mycobacterial infection, chronic rejection, and persistent renal failure. He was transferred to another hospital where belatacept was not available after receiving only two induction doses. Persistent infection (mycobacterial pulmonary infection and fungal and bacterial sepsis) upon readmission here dissuaded us from resuming belatacept treatment.

We compared creatinine trends in belatacept-treated patients with historical and contemporary patients who also developed renal insufficiency, but did not receive belatacept.

Excluding the patient who died, creatinine decreased from baseline 3.1 (1.9–9.4) to 1.7 (1.1–2.5) ($P = 0.05$) at 1 month, 1.9 (1.7–2.0) ($P = 0.13$) at 3 months, and 1.9 (1.1–2.0) ($P = 0.03$) at 6 months. The historic cohort's baseline creatinine value was 3.2 ($n = 66$; IQR 3.0–3.8; none dialysis-dependent) and the follow-up value was 2.6 ($n = 66$; IQR 2.1–3.4; none dialysis-dependent) (test for difference in creatinine change $P = 0.48$) (Fig. 1). Nephrotoxicity in controls who did not receive belatacept was predominately related to calcineurin toxicity.

Including the patient who died, the belatacept cohort's median creatinine value at baseline was 3.7 and 1.9 at follow-up. The historic cohort's baseline creatinine value was 3.2 ($n = 66$; IQR 3.0–3.8; none dialysis-dependent) and the follow-up value was 2.6 ($n = 66$; IQR 2.1–3.4; none dialysis-dependent) (test for difference in creatinine change $P = 0.28$).

Table 3. Relationship between renal and lung function (next page)

	1Mo before Belatacept	Belatacept initiation	1Mo after initiation	3Mo after	6Mo after
Patient 1					
Cr	2.1	2	2.5	1.9	2
GFR	24	25	21	28	25
FEV1	1.05	1.06	1.01	0.96	0.97
Renal replacement	No	No	No	No	No
FK level	11.3	11.6	6.2	2.9	2.1
Cyclo level					
Rapa level					
Patient 2					
Cr	2.34	1.92	2.42	1.76	1.98
GFR	20	26	20	29	25
FEV1	1.29	1.21	1.22	1.23	1.26
Renal replacement	No	No	No	No	No
FK level	7.4	6.2	7.5	2	2
Cyclo level					
Rapa level	0	0	0	5.2	4.3
Patient 3					
Cr	2.2	3.1	2.68	2.02	1.94
GFR	31	21	25	32	37
FEV1	2.2	2.55	2.6	2.58	2.57
Renal replacement	No	No	No	No	No
FK level	4.7	1.6	3.2	1	1
Cyclo level					
Rapa level	0	0	0	6.9	3.2
Patient 4					
Cr	0.97	4.3	1.08	1.67	1.9
GFR	60	14	60	41	36
FEV1	1.39	1.88	1.72	1.86	1.6
Renal replacement	No	No	No	No	No
FK level	2	3.1	2.4	8.8	5.3
Cyclo level					
Rapa level	3.5	1			9.7
Patient 5					
Cr	1.94	1.82	1.65	1.96	1.72
GFR	25	24	28	25	30
FEV1	1.45	0.88	0.87	0.91	0.95
Renal replacement	No	No	No	No	No
FK level	0	0	7.4	7	4.8
Cyclo level	218	61	0	0	0
Rapa level					
Patient 6					
Cr	0.78	On Dialysis	0.81	On Dialysis	0.67
GFR	60	31	60	19	60
FEV1	1.12	0.9	1.08	1.03	0.98
Renal replacement	No	Yes	No	Yes	No
FK level	19.3	6.5	0	0	0
Cyclo level	0	0	276	94	74
Rapa level	0	0	0	10.3	5.2
Patient 7					
Cr	1.5	On Dialysis	On Dialysis	On Dialysis	Deceased
GFR	55	On Dialysis	On Dialysis	On Dialysis	Deceased
FEV1	1.54	On Ventilator	On Ventilator	On Ventilator	Deceased
Renal replacement	No	Yes	Yes	Yes	
FK level	1.7	9.4	5	3.5	

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Table 3. Continued.

	1Mo before Belatacept	Belatacept initiation	1Mo after initiation	3Mo after	6Mo after
Cyclo level					
Rapa level	5.5	0	0	17.4	
Patient 8					
Cr	1.01	On Dialysis	1.72	0.99	1.08
GFR	60	6	60	60	60
FEV1	1.5	1.72		1.78	1.87
Renal replacement	No	Yes	No	No	No
FK level					
Cyclo level	0	20	0	0	0
Rapa level	13.5	4.5	19.1	14.9	10.9

1Mo before, 1 month before belatacept was started; Belatacept, belatacept initiation; 1Mo after, 1 month after belatacept initiation; 3Mo after, 3 months after belatacept initiation; 6Mo after, 6 months after belatacept initiation; FK level, tacrolimus level; Cyclo level, cyclosporine level; Rapa level, rapamycin level.

Changes in lung function

Among seven surviving patients, lung function, by serial FEV_1 measurements, remained stable at 1, 3, and 6 months, respectively, after belatacept initiation, as shown in Table 3, with baseline FEV_1 1.2 l/s (0.9–1.9); 1.2 (1.0–1.8) ($P = 0.93$); 1.2 (1.0–1.9) ($P = 0.80$); and 1.3 (1.0–1.9) ($P = 0.90$).

FEV_1 in belatacept patients is compared with historic controls. Median historic cohort FEV1 median change was −2.2%; belatacept cohort FEV1 median change was −1.3% (Fig. 2).

Immunosuppression changes

Tacrolimus levels decreased from baseline [4.7 mg/dl (0.8–8.0)] through 1-month [4.1 (1.2–6.8) ($P = 0.82$)], 3-month [2.5 (0.5–5.3) ($P = 0.55$)], and 6-month follow-up [1.5 mg/dl (0–3.5) ($P = 0.19$)] following belatacept initiation, although the reduction observed was not statistically significant.

Acute rejection and infection

One patient was diagnosed with mild acute cellular rejection (A1) 3 weeks after starting belatacept, and responded to three doses of IV methylprednisolone with negative subsequent biopsies. No other patient had acute rejection or was treated with augmentation of immunosuppression. Three patients (#4, 6, and 7) had recurrent bacterial infections with organisms identified in those patients before belatacept administration (Pseudomonas aeruginosa and Mycobacterium avium complex). Two patients (#5, 8) developed *de novo* antibiotic-responsive infections with Klebsiella, Enterobacter cloacae, and Pseudomonas pneumonia. Additionally, two patients were diagnosed with seasonal influenza A 2 (#6) and 4 months (#4) after belatacept initiation. Three patients had no infectious complications. CMV and post-transplant lymphoproliferative disease were not detected in this cohort during 6-month follow-up.

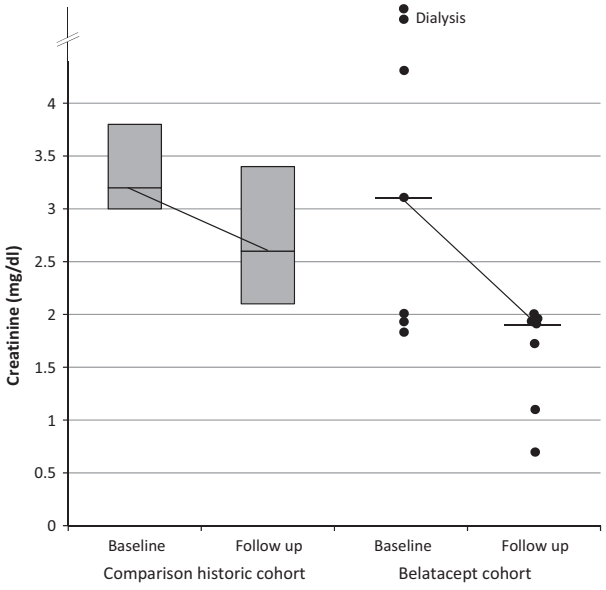

Figure 1 Median creatinine at baseline and a 6-month follow-up by cohort. Left: box represents IQR; line represents median. Number of patients included: baseline: 66 and follow-up: 66. Right: dots represent patient values; lines represents median. Number of patients included: baseline: 7 and follow-up: 7. One belatacept cohort patient on hemodialysis and mechanical ventilation was not included because he died prior to 6 months. Two patients from the belatacept cohort included here were on hemodialysis at baseline, and no patients were on hemodialysis at follow-up.

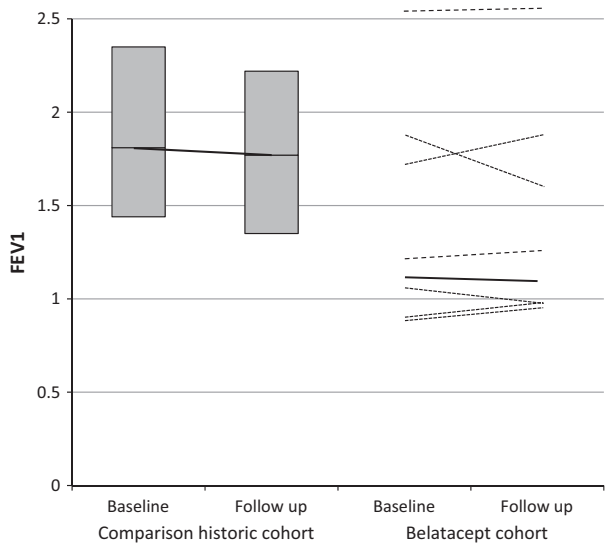

Figure 2 Median FEV_1 at baseline and a 6-month follow-up by cohort. Left: box represents IQR; line represents median. Right: short-dotted lines represent single-lung transplants. Dotted lines represent double-lung transplants. Bold line represents medians. The patient on mechanical ventilation is not represented in this figure but was to calculate the median value.

We compared the infections rate in belatacept-treated patients with historic controls. The infection rate (number of infections/days followed) was about half in the belatacept patients versus the control patients (0.18 events/30 days vs. 0.3, respectively; $P = 0.09$).

Discussion

Immunosuppressive drug toxicity continues to represent a major challenge after lung transplantation. Both cyclosporine and tacrolimus have a relatively narrow therapeutic index.

Progressive deterioration in renal function after lung transplantation contributes substantially to morbidity and mortality and is largely attributable to CNI-related nephrotoxicity [9]. The prevalence of chronic kidney insufficiency is 23.7% within 1 year, 36.7% within 5 years, and 75.4% within 10 years of transplantation [10]. According to UNOS (United Network for Organ Sharing) registry data, dialysis or renal transplantation is performed in 1.8% of patients by 1 year, 4% within 5 years, and 14.4% within 10 years [1].

In our retrospective analysis of our experience to date, belatacept treatment in eight lung transplant recipients with acute renal failure or refractory renal insufficiency was associated with improvement in renal function, and allowed reduction in CNI exposure without evidence of increased immune-mediated lung injury. Two of the three cases requiring dialysis before belatacept were no longer dialysis-dependent on the belatacept and reduced CNI regimen described in our study. Lung function remained stable in all but one case after belatacept despite substantial CNI reduction. Although we have treated only a small number of cases and our experience is uncontrolled, we consider it unlikely that the observed improvement in renal function and reduced CNI and mTOR inhibitor exposure could have been safely achieved without belatacept coverage. Compared with the historic controls managed conventionally with CNI reduction alone, the patients in our belatacept cohort experienced a greater although not clinically significant improvement in the renal function.

Thus based on our experience to date, belatacept combined with CNI reduction warrants further study as an approach to confirm safety and efficacy for managing delayed-onset renal insufficiency in lung transplant patients.

The majority of patients in the belatacept cohort were older than 65 years. This reflects our transplant population (43% are older than 65 at the time of transplantation).

CNI causes reduction in GFR through direct toxic effects on the renal vasculature by inducing vasoconstriction in the afferent preglomerular arteriole [2,6]. CNI nephropathy is typically dose-related, and sometimes reversible with CNI reduction or withdrawal. A reduction in CNIs in renal transplant recipients with histological evidence of nephropathy has been reported to result in sustained improvement of renal function [11]. Similar results were reported for heart and liver transplant patients who received reduced CNI intensity or CNI-free immunosuppression [12,13]. Although use of anti-mitotic agents (mycophenolate mofetil or azathioprine) and steroids along with a CNI is associated with an improved therapeutic index, acute renal insufficiency remains common in the first years after transplant, and chronic renal insufficiency is prevalent subsequently, in our hands and in registry data.

Belatacept is a fusion protein composed of the Fc fragment of a human IgG1 immunoglobulin linked to the extracellular domain of CTLA-4, developed to provide effective immunosuppression and has been approved for clinical use as a renal-protective alternative to CNIs. It was designed to block CD28, a critical activating receptor on T cells, by binding and saturating its ligands B7-1 and B7-2. Belatacept was approved initially for clinical use for prophylaxis of acute kidney allograft rejection in adults (FDA in June 2011). Reports suggest that belatacept may also be useful in kidney, liver, and

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perhaps other organ transplant recipients with pretransplant renal insufficiency to avoid additional renal injury associated with CNI's, as a strategy to protect the allograft from immune injury while renal function recovers [14–16]. Recently, LaMattina *et al.* [17] reported our institutional experience with seven liver transplant patients who received belatacept and mycophenolic acid maintenance immunosuppression. They suggest that a CNI-free immunosuppressive regimen combining belatacept with mycophenolic acid may be safe maintenance immunosuppression regimen in hepatitis C-positive liver transplant recipients with renal dysfunction.

The role of blocking the CD28-B7 cell costimulatory pathway for obliterative bronchiolitis development was investigated in a murine heterotopic airway transplantation model [18]. The development of obliterative changes in airways involved both CD28/B7-dependent and CD28/B7-independent processes and can be inhibited by CTLA4IgG (belatacept is second generation of CTLA4IgG). Tikkanen *et al.* [19] in 2002 describe the importance of the CD28/B7-2 costimulatory pathway in regulating proinflammatory cytokine responses and initiation of chronic rejection that may ultimately lead to obliterative bronchiolitis after lung transplantation in rats. CTLA4IgG fusion protein, which blocks both CD28/B7-1 and CD28/B7-2 interaction, significantly delayed the development of epithelial injury and airway occlusion. We have found one case report describing a beneficial effect of belatacept use after lung transplantation [20].

Additional studies will be necessary to evaluate whether belatacept is safe and effective as part of a systematic strategy to limit CNI exposure in lung and other transplant recipients who develop or are at high risk for renal insufficiency following transplantation, and to develop evidence based to inform development of best practice for its use in these populations. Our belatacept treatment experience was generally associated with stable lung allograft function during the study interval despite markedly reduced exposure to conventional IS.

Using in place of CNI-based IS in kidney transplant recipients, several belatacept-based regimens were each associated with higher rates of acute rejection than CNI-based conventional regimen [15,21]. Based on this and our own experience, we generally chose to limit the duration of or avoid complete discontinuation of CNI or mTOR after belatacept initiation. Instead we most often targeted lower trough levels of one or more conventional IS drugs. That only one of our patients was diagnosed with steroid-responsive acute cellular rejection while temporarily off of CNI is anecdotal evidence in support of that approach.

Although patient demographics are heterogenous in this small case series, baseline immunosuppressive regimens are similar consisting of a CNI and prednisone. Two patients were on inhaled cyclosporine at the time of starting belatacept. In all but one patient who received belatacept with a standard CNI regimen, both creatinine and FEV_1 were stable or improved during 6 months of follow-up.

Infections did not appear to have increased during belatacept and CNI reduction, and most of our patients who were treated for recurrent or newly diagnosed infections responded promptly to conventional antimicrobial treatments. Our single unfavorable experience in a patient with pre-existing atypical mycobacterial infection is similar to our other experiences in AFB-infected patients treated only with conventional IS, and probably is not attributable to that patient's limited belatacept exposure. We presented results for GFR without this patient because he was on dialysis or deceased at all measurement points. Since his renal function was always unmeasured and poor, including him in the analysis could change no findings except for pushing *P*-values more in the direction of nominal significance. Nonetheless, until the risk/benefit ratio for this new medication becomes better defined in the setting of complex, high-risk patients, great caution would seem appropriate in monitoring for malignancy or chronic colonization with multidrug-resistant organism, fungus, or mycobacteria.

Our study is limited in that it is a retrospective single center experience based on a small number of individual patients managed outside of any formal protocol and with relatively short-term follow-up. Importantly, we cannot exclude the possibility that similar results might have been achieved without belatacept use. However, in comparison with other patients we have managed without belatacept, anecdotally we would have predicted less satisfactory recovery of renal function had CNI weaning been less aggressive, and a higher incidence of acute rejection and/or deterioration in lung function if we had targeted similarly low levels of CNIs or mTOR exposure. The decision to start (and stop) belatacept and regarding how to manage other IS agents was not driven by predetermined selection criteria, but was based on individual clinician discretion, and thus is not necessarily readily generalizable. Nonetheless, our small series supports the hypothesis that belatacept enables safe transient or even longer-term reduction in dosing of nephrotoxic conventional immunosuppressants.

Our study is a single center case series including eight subjects having a 6-month follow-up. Although there were notable differences in demographics and immunosuppression management in our series, stability of renal and lung function was observed up in all but one case. Greater experience using belatacept in larger numbers of lung recipients and controlled clinical trials are required to better define the risks and benefits of belatacept combined with lower doses of CNI protocols on graft and renal function.

In conclusion, our results suggest that lung transplant recipients who develop renal insufficiency may be safely managed using belatacept to lower doses of conventional immunosuppression. Our results are consistent with previous studies performed in kidney and liver transplant patients that showed a renal-sparing effect associated with treatment with belatacept and CNI reduction. Further clinical trials are necessary to assess belatacept's effects definitively in the lung transplant population.

Authorship

IT: involved in study design, data collection and writing the paper. MT: involved in data analysis and writing the paper. EB: involved in data collection, data analysis and writing the paper. PS: involved in study design, data analysis and writing the paper. JK: involved in writing the paper. RR: involved in data analysis and writing the paper. EdB: involved in writing the paper. BR: involved in data collection and writing the paper. KR: involved in data collection and writing the paper. BG: involved in data collection and writing the paper. SP: involved in data collection and writing the paper. RNP: involved in study design and writing the paper. AI: involved in study design, data analysis and writing the paper.

Funding

Supported by Pulmonary Fibrosis Foundation Grant #1007241; A Iacono.

Acknowledgements

The authors would like to thank Sharrief McGee RN and Teresa Hughes RN BSN for their ongoing dedication in the management of lung transplant recipients in this study.

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