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Experience with Alpha-1 Proteinase Replacement Post-Lung Transplantation in Alpha-1 Antitrypsin Deficiency: A Single Center Case Series

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Abstract

Alpha-1 antitrypsin deficiency (AATD) accounts for approximately 5% of lung transplants (LTx) performed annually. No studies have addressed the potential benefit of ongoing alpha-1 proteinase inhibitor (A1-PI) replacement to AATD patients post-LTx. Our primary objective was to assess potential benefits of continually administering A1-PI from pre- to post-transplantation for AATD LTx recipients. A retrospective case series was performed on AATD LTx recipients between 2002 and 2018. Data reviewed included date of A1-PI initiation, pulmonary function tests, and surveillance bronchoscopies. Endpoints included the change of forced expiratory volume in one-second (FEV1), infective episodes, chronic lung allograft dysfunction (CLAD), and acute rejection episodes. Out of the 13 AATD LTx recipients, 6 continually received A1-PI beginning prior to transplant (Group 1), and 7 were re-introduced to A1-PI a number of years after LTx (Group 2). After two years, Group 1 experienced a median FEV1% predicted decline of 0.0%, and Group 2 experienced a median decline of 15.0%. No differences noted in frequency of infective episodes. One patient in Group 1 developed CLAD

about 2.5 years post-LTx, whereas all Group 2 patients developed CLAD at a mean of 5.4 years post-LTx. No Group 1 patients experienced acute lung rejection episodes noted from surveillance bronchoscopies, corresponding data not available for Group 2. We report that the continual use of A1-PI in AATD LTx recipients is associated with better maintenance and stabilization of lung function and potentially less acute lung rejection episodes early post-LTx. Prospective studies should be performed to confirm possible benefits.

Keywords
Lung transplant; alpha-1 antitrypsin deficiency; alpha-1 proteinase inhibitor replacement

1. Introduction

Chronic obstructive pulmonary disease (COPD) from alpha-1 antitrypsin deficiency (AATD), accounts for 4.7% of all lung transplant (LTx) recipients, according to the International Society of Heart and Lung Transplantation (ISHLT) report [1]. Not all lung transplant centers perform AATD phenotype and serum value testing to rule out the genetic potential. Hence the number of AATD not tested in the "COPD" labeled group for ISHLT is unknown. Recent data show more favorable long-term outcomes among LTx recipients with AATD compared to those with non-AATD COPD [2]. In the pre-transplant phase, it has been established that patients with AATD and confirmed lung obstruction have a more rapid decline in lung function compared to alpha-1 antitrypsin sufficient [3-5]. However, the rate of lung function decline post-LTx has not been fully delineated with or without continuation of alpha-1 proteinase inhibitor (A1-PI) replacement therapy in the AATD LTx recipients. Banga and colleagues described the natural history of the lung function for LTx recipients with AATD and compared them to the COPD group [6]. The two primary endpoints were FEV_1% predicted and episodes of any rejection. Although there were no differences observed between the two groups, it should be noted that only 13% of the AATD LTx recipients received A1-PI therapy post-LTx.

A1-PI protects lung tissue against the action of proteolytic enzymes, including neutrophil elastase, cathepsin G and serine proteinase 3 [7, 8]. A1-PI can also decrease inflammation by binding to and inactivating interleukin-8 (IL-8) [7, 9]. Similarly, azithromycin has been widely studied and demonstrated the benefits of lessening the risk of rejections and chronic lung allograft dysfunction (CLAD) by blocking the IL-8 pathway and reducing the degree of airway neutrophils [10-12]. The role of A1-PI appears to go beyond anti-inflammatory and anti-infective benefits. In addition to the potent inhibitor properties against the proteolytic enzymes, A1-PI has immune modulation function in animal models, particularly in pancreatic (islet) cell transplantation [13-15]. Infusion of recombinant alpha-1 antitrypsin prolongs islet cell allograft survival in mice through an improved immune tolerance mechanism [13-15]. Iskender and colleagues utilized A1-PI to attenuate reperfusion injury after prolonged hypothermic preservation [16]. They showed that treatment with A1-PI suppressed inflammatory responses and improved graft function post-transplant.

Therefore, it is postulated that LTx recipients for AATD who are continued on A1-PI post lung transplantation should have less acute cellular rejection episodes and a better maintenance of their lung function. Here we present a case-controlled series to account for the differences seen in

transplant outcomes between AATD LTx recipients who were continued on A1-PI compared to historical controls who had interruption in the A1-PI following lung transplantation.

2. Methods

2.1 Study Design

A retrospective single center case series of lung transplant recipients at UC San Diego Health System who received lung transplantation for AATD between the years 2002 and 2018 was performed. Patients were identified through our transplant database and the electronic medical record. Approval was received from the University of California San Diego Institutional Review Board (#200906), along with a waiver of informed consent prior to data collection. Demographic data collected includes age at transplant, type of LTx, AATD phenotype, alpha-1 antitrypsin serum level, date of initiation of A1-PI, pulmonary function tests, associated hypogammaglobulinemia, gastroesophageal reflux disease (GERD), photopheresis treatments, antibiotic data, and available surveillance bronchoscopy data. Endpoints included the change of forced expiratory volume in one-second (FEV_1) post-transplant, infective episodes, acute cellular lung rejection episodes, and chronic lung allograft dysfunction (CLAD) staging.

Two groups were identified: Group 1 patients had continuous use of A1-PI post-LTx vs. Group 2 patients who had not been identified to have AATD until after transplant, or had an interruption in the A1-PI therapy post lung transplantation. Group 1 patients were transplanted between 2016-2018, following a change of our treatment protocols, while the Group 2 patients were transplanted between 2002-2011. In 2015, testing for AATD phenotype and serum levels for all COPD patients referred for lung transplantation became routine practice. Several patients on the active waitlist with the diagnosis of COPD were corrected to the diagnosis of AATD, if found to have the deficiency. Triple drug immunosuppression with tacrolimus, mycophenolate mofetil, and corticosteroids had been provided to all LTx recipients. All patients in Groups 1 and 2 (besides Patient 1B) received azithromycin 250 mg daily following LTx. Additionally, all patients received prophylaxis for pneumocystis pneumonia, cytomegalovirus, and aspergillus post-lung transplant. Routine surveillance with chest images and spirometry had been provided on all patients. All patients were screened for antibiotics and photopheresis treatments during A1-PI therapy. In 2016, the UC San Diego Lung Transplant Program made changes to the induction protocol; from no induction to universal induction with basiliximab, unless there were clinical contraindications. Additionally, in 2016 we began performing surveillance bronchoscopies with transbronchial biopsies to identify asymptomatic acute cellular rejection episodes. Surveillance bronchoscopies were performed at week 6 and months 3-, 6- and 12.

Since Group 1 patients were only an average of two years post-LTx at the time of this analysis, the pulmonary function test data analyzed for all patients only included the first two years post-LTx. Patients were staged for CLAD utilizing FEV_1 values following the 2019 definition: CLAD 0 >80% of baseline, CLAD 1 66%-80% of baseline, CLAD 2 51%-65% of baseline, CLAD 3 35%-50% of baseline, and CLAD 4 <35% of baseline [17]. For this study, we will be referring to the bronchiolitis obliterans syndrome (BOS) phenotype of CLAD, a clinically obstructive disease presenting with declining FEV_1 values. Given the irreversible nature of this disease, the primary objective was to determine if there is a potential benefit in administering A1-PI post-transplant in selected recipients.

3. Results

Between January 1, 2002 and December 31, 2018, our center performed 330 lung transplants. Of these recipients, 13 patients underwent LTx for AATD, accounting for 3.9% of our cohort. Out of the 13 AATD LTx recipients, 6 continually received A1-PI beginning prior to transplant (Group 1), and 7 historical control patients were re-introduced to A1-PI a number of years after LTx (Group 2). The mean age at initiation of A1-PI for Group 1 was 56.2 years (range: 39.3 – 69 years) and for Group 2 was 61.2 years (range: 49 – 69 years). The median time elapsed from LTx to A1-PI initiation for Group 2 was 6.8 years (range: 0.7 – 10.5 years). Of the six Group 1 patients, three patients received a single LTx and three received a double LTx. Of the seven Group 2 patients, four patients received a single LTx, and three received a double LTx. The phenotype breakdown included: 8 PiZZ, 3 PiSZ, 1 PiMZ and 1 PiMF. All patients initiated treatment between 2009 and 2018 and received A1-PI with Glassia, Prolastin-C, or Zemaira at a dose of 60 mg/kg intravenous once weekly. Three patients in each group had associated hypogammaglobulinemia. Four of the Group 1 patients and six of the Group 2 patients have been diagnosed with GERD. None of the patients in Group 1 received photopheresis treatments, and four of the Group 2 patients underwent photopheresis treatments. A baseline characteristics summary of Groups 1 and 2 are presented in Table 1 and detailed patient-specific baseline characteristics are presented on Table 2.

Table 1 Summary table comparing baseline characteristics between Groups 1 and 2.

	Group 1: A1-PI Continued Post-LTx (n=6)	**Group 2: A1-PI Interruption (n=7)**
Demographics:		
Age (mean years)	56.2	61.2
Male (%)	5 (83.3)	6 (85.7)
BMI (mean kg/m^2)	24.8	22.8
Race:		
Caucasian (%)	6 (100.0)	7 (100.0)
Single or Bilateral Lung Transplant:		
Single	3 (50.0)	4 (57.1)
Bilateral	3 (50.0)	3 (42.9)
Induction Agent:		
Basiliximab (%)	4 (66.7)	0 (0.0)
None (%)	2 (33.3)	7 (100.0)
Outcomes Post-LTx:		
Primary Graft Dysfunction (PGD) Stage 0 at 72 hours	6 (100.0)	7 (100.0)
Days on Ventilator (mean)	1.0	1.3
Days in ICU (mean)	4.7	4.0
Years to A1-PI Initiation (median)	Continuous	6.8 (range: 0.7-10.5)
1-Year Survival (%)	6 (100.0)	7 (100.0)

Table 2 Detailed baseline demographics, changes in FEV_1 and FEV_1% predicted values two years post-baseline value, and CLAD staging at two years post-LTx for all AATD patients. Patients 1F and 2D were excluded in the two-year calculations due to a lack of adequate data.

Patients	Age (at A1-PI initiation)	AATD Allele	Serum AAT Level at Baseline (mg/dL)	Transplant to A1-PI (Years)	Single or Double Lung Transplant	Associated Hypogamma-globulinemia	GERD	Photopheresis Treatments	FEV_1 Change in First 2 Years Post-Baseline (%)	FEV_1% Predicted Change in First 2 Years Post-Baseline (%)	CLAD Stage at 2 Years Post-LTx
Patient 1A	53.0	ZZ	Unknown	N/A	Single	Yes	Yes	No	-11.0	-3.5	0
Patient 1B	60.0	ZZ	47	N/A	Double	Unknown	Yes	No	0.0	0.0	0
Patient 1C	69.0	SZ	Unknown	N/A	Single	Yes	No	No	-23.0	-21.0	0
Patient 1D	39.3	ZZ	Unknown	N/A	Double	No	No	No	5.7	6.1	0
Patient 1E	57.0	MZ	127	N/A	Single	No	Yes	No	0.0	0.0	0
Patient 1F	59.0	ZZ	84	N/A	Double	Yes	Yes	No	N/A	N/A	N/A
Patient 2A	62.0	ZZ	22	10.5	Double	Yes	Yes	Yes	-18.0	-13.5	0
Patient 2B	56.8	MF	Unknown	6.8	Single	Yes	Yes	No	-18.0	-16.0	0

Patient 2C	61.6	ZZ	<30	3.0	Double	Unknown	Yes	No	-15.0	-14.0	0
Patient 2D	65.9	ZZ	<30	6.7	Single	Unknown	No	No	N/A	N/A	N/A
Patient 2E	69.0	SZ	94	10.2	Single	Unknown	Yes	Yes	-8.5	-13.5	0
Patient 2F	49.0	ZZ	<30	7.0	Single	Yes	Yes	Yes	-24.0	-24.5	0
Patient 2G	64.1	SZ	<30	0.7	Double	Unknown	Yes	Yes	-64.5	-63.5	4

Overall, at two years post-baseline FEV_1, Group 1 (excluding Patient 1F) experienced a median FEV_1% predicted decline of 0.0% (range: -21.0 – 6.1%), while Group 2 (excluding Patient 2D) experienced a median decline of 15.0% (range: 13.5% – 63.5%), Table 2 and Figure 1. Only one patient in Group 2 (Patient 2G) was re-introduced to A1-PI during the two-year post-baseline timeframe. Patients 1F and 2D were excluded from the overall analysis due to a lack of adequate data. Of the six Group 1 patients, Patient 1F did not reach two years post-baseline. Patient 1F passed away due to septic shock about 1.5 years post-LTx. The last recorded pulmonary function test was at 7 months post-baseline with 4% improvement in FEV_1% predicted. Patient 2D did not have any pulmonary function test data points until 32 months post-baseline FEV_1. Due to the small sample size, we were unable to see a difference between the various AATD genotypes.

No differences were noted in frequency of infective episodes between Groups 1 and 2. All patients between Groups 1 and 2 experienced at least two infective episodes during the first two years post-LTx. Group 1 patients experienced a mean of 3.5 infective episodes (range: 2-8), and Group 2 patients experienced a mean of 3.9 infective episodes (range: 2-7). To note, persistent/repeated infections were counted as one infective episode in the averages noted above. The persistent/repeated infective episodes occurred in three out of the thirteen total patients (Patients 1A, 1E, and 2F). Patient 1A experienced persistent viral infections of coronavirus and rhinovirus, Patient 1E experienced persistent Klebsiella pneumonia for nearly one year, and Patient 2F experienced recurrent left lower lobe pneumonia and bronchiectasis.

All patients were staged for chronic lung allograft dysfunction (CLAD), bronchiolitis obliterans syndrome (BOS) phenotype, utilizing FEV_1 values from pulmonary function test data based on the ISHLT guidelines. Only one patient (Patient 1C) in Group 1 developed CLAD 1 about 2.5 years post-transplant, whereas all Group 2 patients developed CLAD 1 at a mean of 5.4 years post-transplant (range: 0.7-8.0 years). Patient 2C went from CLAD 1 to CLAD 0 four years after starting A1-PI. Of the Group 2 patients that developed CLAD 2, it was a mean of 12.75 years post-transplant (range: 9.5-16.5 years). The Group 2 patients that developed CLAD 3 was a mean of 12.0 years post-transplant (range: 11.5-12.5 years) and a mean duration of 4.4 years post-baseline for those that developed CLAD 4 (range: 1.3-7.5 years). At two years post-LTx, all patients were CLAD 0, besides Patient 1G who was CLAD 4, Table 2.

Surveillance bronchoscopies with transbronchial biopsies were only performed on Group 1 patients given the changes in clinical practice. No Group 1 patients experienced any acute cellular lung rejection episodes. Corresponding surveillance bronchoscopy data are not available for Group 2 as they did not undergo surveillance bronchoscopies at that time period.

4. Discussion

Observational studies and surveys of transplant centers have shown that 13-21% of AATD lung transplant recipients receive augmentation therapy at some point following transplant, but the clinical experience has not been clearly reported in the current literature [6, 18, 19]. A review of the world-wide lung transplants through the ISHLT Registry shows that the patients with AATD tend to do worse immediately after the post-operative period, making perioperative A1-PI replacement therapy appealing. From January 1995 to June 2018, a total of 63,530 transplants occurred world-wide. 2,969 transplants (4.7%) were performed for patients with AATD [1]. Within the United States, AATD LTx recipients compared to COPD LTx recipients were younger (mean age 50.5 years vs. 58

years) and consisted of slightly more male gender [19]. AATD LTx recipients were more likely to be treated for rejection in the first year post-LTx (57% vs. 49%), have a higher rate of airway dehiscence (2.1% vs. 0.7%), and die from an infectious complication (23% vs. 15%) compared to COPD LTx recipients [20].

In a single center study at the Cleveland Clinic, Banga and colleagues described lung function findings in 45 AATD double LTx recipients as compared to 231 COPD counterparts [6]. Despite a younger age of lung transplantation, there was a lower one year survival (73%) in the AATD group when compared to COPD group (86%). Interestingly, there was no significant difference in rejection or survival between the two groups. An important notation is that only 6 out of the 45 patients with AATD had augmentation therapy re-initiated after lung transplant. There was an interruption in the augmentation therapy around the time of transplantation, even in the cases where therapy was continued post-transplant.

Previous studies have shown similar decline in FEV_1 in AATD patients post-LTx compared to COPD patients and no differences in early or late mortality; however, AATD patients with a history of double LTx appeared to have a faster decline of FEV_1 when compared to COPD patients ($p<0.002$) [6].

Current research is very limited regarding the value of A1-PI therapy on FEV_1 values, with most of the data suggesting that there is no significant difference in the change of FEV_1 values for pre-LTx patients who are receiving A1-PI therapy [21-26]. However, the initial observational trials for A1-PI therapies were not powered properly to yield the required statistical basis for patients outside of the FEV_1 categories between 35-75%. In the RAPID (Randomized, Placebo-controlled Trial of Augmentation Therapy in Alpha-1 Proteinase Inhibitor Deficiency) study, patients with AATD treated with augmentation therapy exhibited lower annual rate of lung density changes compared to placebo [21]. CT densitometry was chosen as the radiographic changes are more accurately reflected compared to the slower changes noted with spirometry [27]. Prospective studies are still needed to evaluate further the potential use of augmentation for both pre- and post-transplant in alpha-1 antitrypsin deficient patients. Additionally, the optimal time to begin therapy and the duration therapy remains unanswered. The higher risk of rejection episodes, airway dehiscence and infectious complications noted in the United Network for Organ Sharing (UNOS) analysis argue for continued A1-PI use [20]. In our single-center case series, the continual use of A1-PI starting pre-LTx in AATD LTx recipients may result in better maintenance and stabilization of lung function and potentially fewer acute cellular rejection episodes.

It is important to weigh the potential cost of initiating A1-PI against the benefits. The 2019 Centers for Medicare and Medicaid Services (CMS) fee schedule estimates that each weekly one-hour infusion of a dose of 60 mg/kg for a 70 kg patient would cost approximately $2,000 (including the procedural cost of infusing the medication) [28, 29]. Thus, the yearly cost exceeds $100,000 per patient at the recommended weekly dosing schedule. However, various costs to weigh against that of the weekly A1-PI infusions include, but are not limited to, the cost of re-transplant, the cost of organ rejection, and poor quality of life. According to Milliman Research Report, published on the UNOS website, the estimated average billed charges in the U.S. in 2017 was $861,700 per single LTx, and $1,190,700 per double LTx [30]. Additionally, the estimated cost of an organ rejection episode can add up to over $13,000 according to CMS pricing guidelines, U.S. Census Bureau, and the U.S. Department of Health and Human Services [28-32].

There are important limitations in our analysis. Most transplant centers do not continue A1-PI therapy post-LTx. As a result, this is a small, single-center, retrospective cohort study. Due to the retrospective nature and small sample size, we were unable to perform statistical analysis on all factors that may result in the progression of lung disease, including rejection, type of lung transplant, and infection. Secondly, the routine testing of alpha 1-antitrypsin deficiency became uniform in our practice in 2015. There are perhaps older recipients that have passed away with COPD who may have had AATD. Third, there are inherent differences observed in the post-transplant management between the two groups compared in this study due to the difference in treatment protocols, which may introduce possible bias. These differences include the use basiliximab induction therapy and surveillance biopsies being performed in Group 1.

In summary, we report that the continual administration of A1-PI beginning pre-LTx, as opposed to the interruption post-LTx, can result in greater maintenance of lung function following a LTx. Mechanistically speaking, there is potential for A1-PI therapy to help reduce acute cellular rejection episodes and subsequently the development of CLAD. Prospective studies should be performed to confirm a benefit in this population on a larger scale.

Author Contributions

Kamyar Afshar, DO: study concept and design, data analysis, manuscript writing/editing. Michelle N. Bremer: data collection, data analysis, manuscript writing/editing. Bharath Ravichandran: study concept, manuscript editing. Ashley A. Feist: data analysis, manuscript editing. Eugene Golts: study concept and design, manuscript editing. Elizabeth H. Schonhoft: study design, manuscript editing. Gordon Yung: study concept and design, data analysis

Competing Interests

There is no personal or financial support or author involvement with organization(s) with financial interest in the subject matter of this article

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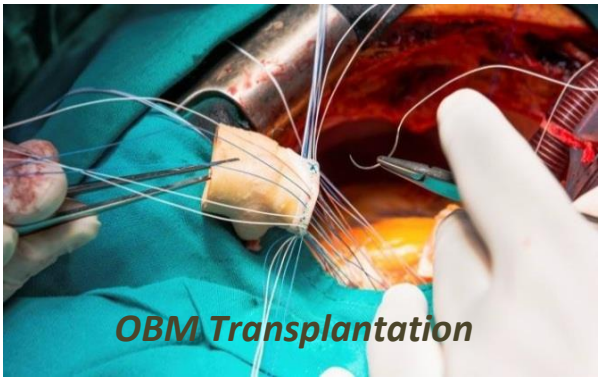

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