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Progression of native lung fibrosis in lung transplant recipients with idiopathic pulmonary fibrosis

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Summary
Background: Single lung transplant recipients with idiopathic pulmonary fibrosis provide an opportunity to study fibrosis in the native lung over time in the setting of pronounced immunosuppression. Lung transplant patients are treated with a regimen of steroids, an antiproliferative agent and a calcineurin inhibitor. This represents a much greater immunosuppression regime than the typical treatment for IPF. To determine whether this regimen of high dose immunosuppression would arrest the progression of fibrosis, the high-resolution chest CT scans (HRCTs) of these patients were reviewed.
Methods: HRCTs of 21 patients who underwent single lung transplant for IPF between 1/96 and 1/06 were reviewed. Scans were evaluated by two readers at 6 months intervals, beginning within 1–2 months after transplant. Two calculations were made on the native lung: total volume and percentage of lung affected by fibrosis. Baseline pulmonary function test data was correlated with the immediate post-transplant CT. Patients were followed for an average of 35 months after transplant.
Results: The mean total volume of the native lung just after transplant was 1120 cc. This decreased to 875 cc by 2 years and 691 cc by 4 years after transplant, representing an average decline of 10.8%/year. Initially, 52% of the native lung was affected by fibrosis compared to 92% at 4 years. Excluding scans with 100% of the lung affected by fibrosis, percentage fibrosis increased 11% per year.
Conclusion: Fibrotic disease within the native lung progresses rapidly in single lung transplant recipients with IPF despite prolonged high dose immunosuppression.
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Introduction

Idiopathic pulmonary fibrosis (IPF) is a disease characterized by progressive lung fibrosis that is typically unresponsive to traditional immunosuppressive agents such as steroids.[1] With an average 50% 3-year survival, patients with IPF have a prognosis similar to lung cancer.[2,3] Currently clinical trials are underway to determine the effectiveness of alternative agents, however to date these agents have demonstrated little effectiveness in arresting the progression of fibrosis.[4] The only long-term effective treatment for IPF at this point is lung transplantation with a 50% 5 year survival and with 26% of patients living to 10 years post-transplant.[5]

Single lung transplant recipients with idiopathic pulmonary fibrosis (IPF) provide a unique opportunity to study fibrosis in the native lung over time in the setting of pronounced immunosuppression. At our institution, lung transplant recipients are typically treated with a lifelong regimen of steroids, an anti-proliferative agent (e.g. mycophenolate mofetil) and a calcineurin inhibitor (e.g. tacrolimus). To determine whether this combination of immunosuppressive agents arrests the progression of fibrosis, we performed a quantitative analysis of lung volumes and severity of fibrosis on sequential high-resolution chest CT scans (HRCTs) of these patients following lung transplantation. This paper is the first to perform direct quantitative analysis of progression of fibrosis in this patient population. The National Institutes of Health ''Panther'' trial plans to assess the efficacy of azathioprine, predisone and N-acetylcysteine. The regimen in our patients is arguably a greater degree of immunosupression and would provide insight as to the likelihood of this trial showing a treatment benefit in IPF patients.

Materials and methods

Patients

This single center study was approved by our institutional review board and informed consent was waived. All patients who underwent single lung transplantation for IPF at our center between January 1996 and January 2006 were included in the study. The diagnosis of IPF was made by the criteria delineated by the American Thoracic Society and European Respiratory Society.[6] These criteria primarily include a restrictive defect on pulmonary function tests, typical HRCT findings (peripheral, basilar fibrosis with honeycombing and a paucity of ground glass) and the exclusion of other clinical disorders that could cause similar fibrosis (e.g. collagen vascular disease, drugs, asbestosis). The pathologic diagnosis of usual interstitial pneumonia was confirmed in the explanted lung. Patients whose final pathologic diagnosis was not consistent with IPF were excluded from analysis. Pulmonary function testing was performed in all patients within 3 months prior to lung transplantation.

The post-transplant immunosuppression employed was a standard three-drug regimen consisting of tacrolimus (calcineurin inhibitor), mycophenolate mofetil (anti-proliferative agent) and prednisone. The tacrolimus daily dose was based on serial follow-up of specific trough blood levels; target levels were 10—14 ng/ml until three months post-transplant at which point the target levels were lowered to 8—12 ng/ml. In addition, the specific dose in a particular recipient is constantly being adjusted based on drug interactions, recent rejection history and tacrolimus adverse affects such as renal impairment among other closely monitored factors. Mycophenolate mofetil was initiated on the standard dose of 1000 mg bid with adjustment for decrease in white blood cell count. The immediate post-operative prednisone dose was 20 mg/day. Three months post-transplant the dose was lowered to 15 mg/day and following six months post surgery the dose was adjusted to 0.2 mg/kg. The prednisone dose is also constantly being adjusted for steroid related adverse effects and rejection history.

CT technique

Following transplantation all patients underwent a HRCT within 1—2 months, followed by repeat HRCTs at regular intervals to evaluate for potential transplant complications (e.g. infection, acute or chronic rejection). The scan interval is variable between patients, but is typically at least every 6 months. The severity of fibrosis in the native lung was evaluated using these scans. The immediate post-transplant HRCT was used as the patient's baseline and subsequent scans were evaluated at 6 month intervals.

HRCT scans were performed on either 16 or 64 detector Lightspeed CT Scaners (GE Healthcare, Milwaukee, WI). Three series were typically performed. Inspiratory images were obtained in the supine position at 1 or 2 cm intervals using a section thickness of 1.25 mm (2 detectors $\times$ 0.625 mm). The following parameters were used: pitch 1.0, gantry rotation speed 400 ms, kVp 120 and automatic mA adjustment. Prone and dynamic expiratory images were also obtained, however these images were not used for analysis. Images were analyzed on a Picture Archiving and Communication System (PACS) workstation.

Image interpretation

Images were evaluated by two readers with subspecialty training in pulmonary imaging. Two calculations were performed in the native lung on each scan: total lung volume and percentage of lung involved by fibrosis (Fig. 1). To calculate the total native lung volume, the area of lung at a specific level was calculated on the PACS workstation using the ''free-form region of interest'' tool. This area was calculated throughout the lung at 2 cm intervals. Subsequently, the total native lung volume was calculated by summing the area at each level and multiplying by the distance between each slice (2 cm). To calculate the percentage of lung involved by fibrosis, the same method was used except that only the regions affected by honeycombing and reticulation were selected. These two findings were chosen as they are most specific for fibrosis and are the primary findings used to make a HRCT diagnosis of IPF.[7,8] Ground glass opacity, which also may be seen with IPF, was not included in this measurement as it is a much more non-specific finding and could represent fibrosis

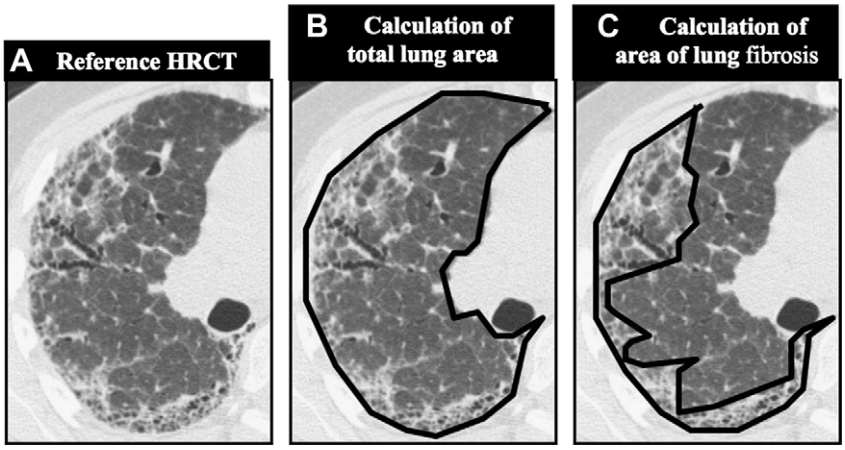

Figure 1 Technique for calculating native lung area and % of fibrosis. Three images are shown, all at the same level. Area is calculated at a specific level (B) by selecting the lung using the ''free-form region of interest'' tool. This is performed at 2 cm intervals throughout the lung. These are summed and multiplied by 2 cm to calculate total lung volume. Calculation of the area of lung fibrosis (C) is accomplished in the same manner except only selecting the regions of reticulation or honeycombing.

below the resolution of CT or active inflammation.[9] The development of ground glass in the native lung was noted by the readers, however, as ground glass opacity may be seen in association with acute exacerbations of IPF. There were three CT scans on which these calculations were unable to be performed and were excluded because of significant pleural effusions.

While this study focuses on abnormalities in the native lung, significant abnormalities in the transplanted were also noted. These were divided into two categories: increased lung attenuation (nodules, ground glass opacity, consolidation, airways inflammation) and decreased lung attenuation (air trapping and mosaic perfusion). The importance of this distinction is that the former most commonly represent acute processes such as acute rejection or infection, whereas the later in this clinical setting is typically due to chronic rejection/obliterative bronchiolitis.

Statistical analysis

Statistical analysis was performed using SAS/STAT software package version 9.1 (SAS Institute, Cary, NC) for Windows (Microsoft, Redmond, WA). Correlations between the baseline pulmonary function tests and the initial post-transplant CT lung volumes and percentage of lung affected by fibrosis were performed using the Spearman's rank-order correlation coefficients. Agreement between the two readers in calculating the percentage of lung affected fibrosis was performed using Pearson correlation coefficients.

Statistical significance of decline in lung volumes over time was performed using a mixed model regression. Since measurements were taken on the same patients over time, they are likely correlated. To accommodate this correlation, mixed model regression was used. Unlike repeated measures analysis of variance, mixed model regression also allows for unbalanced data, use of all available data when some are missing, and can incorporate predictors that change from one time to the next. We fit a model allowing patient specific intercepts and slopes since when looking at plots of the individual patients' lung volumes over time, patients began with different lung volumes and their progression over time appeared to have different rates.

Results

Twenty-one patients underwent single lung transplantation at our center between January 1996 and January 2006 and were included in this study. Patient demographics, in addition to the pre-transplant IPF treatment regimen and pre-transplant pulmonary function tests, are depicted in Table 1. Patients were followed for an average of 35 months after transplant (range 6 months—90 months). The number of patients included in analysis with respect to time after transplant is as follows: immediately post-transplant (21), 1 year (20), 2 years (16), 3 years (12) and 4 years (5). Of these patients, 12 died during the study period, 1 received an additional lung, and 8 were alive at the end of the follow-up period. The number of scans performed after the 4 year post-transplant period was too small to be included in the analysis.

Within the 4 year period after transplant a total of 136 CT scans were evaluated. Results are depicted in Table 2. Progression of disease on HRCT in the native lung in two representative patients is shown in Fig. 2.

Baseline pulmonary function testing, including diffusing capacity of the lung for carbon monoxide (DLCO) and forced vital capacity (FVC), was available on 20/21 patients prior to lung transplant. There was a statistically significant correlation between pre-transplant FVC and the native lung volume calculated on the immediate post-transplant CT ($r = 0.69$, Spearman's rank-order correlation; $p < 0.001$). This is depicted in Fig. 3. Otherwise, no statistically significant differences were seen between the PFT and CT data.

The mean total native lung volume just after transplant was 1120 cc (range 182—1994 cc). This declined to an average of 875 cc by 2 years and 691 cc by 4 years. The average yearly percentage decline in lung volume after

Table 1 Demographics of the 21 single lung transplant patients with IPF. The patients' pre-transplant pulmonary function tests are given including: forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO). The patients' treatment for IPF prior to transplant is also included.

No	Sex	Race	Age at transplant (years)	FVC (liters)	FVC (% predicted)	DLCO (mL/min/mmHg)	DLCO (% predicted)	IPF treatment prior to transplant
1	M	Hispanic	54	1.9	50%	5.3	17%	Prednisone
2	M	Caucasian	46	2.55	52%	16.6	45%	None
3	F	Caucasian	59	1.69	57%	4.15	16%	Prednisone, gamma interferon
4	M	Caucasian	56	1.9	44%	6.9	22%	Gamma interferon
5	M	Caucasian	54	2.4	51%	11.1	82%	None
6	M	Caucasian	59	3.3	68%	7.2	21%	Prednisone, azathioprine
7	M	African-American	54	2.28	54%	9.4	29%	Prednisone, azathioprine
8	F	Caucasian	41	1.9	6%	0.9	24%	Gamma interferon, mycophenolate mofetil
9	M	Caucasian	67	1.3	31%	2.8	9%	Prednisone, mycophenolate mofetil
10	F	Hispanic	62	1.4	60%	4.4	19%	Azathioprine
11	M	Caucasian	52	2.2	40%	8.9	57%	None
12	F	Caucasian	59	1.1	31%	2.9	29%	Prednisone, azathioprine
13	M	Caucasian	51	1.5	31%	8.8	77%	None
14	M	Caucasian	65	2.83	71%	6.4	22%	None
15	M	Caucasian	54	2.2	47%	7.7	49%	Prednisone, azathioprine
16	M	Caucasian	60	2.6	52%	8.6	24%	Prednisone, azathioprine
17	F	Hispanic	38	1.1	40%	4.3	36%	Prednisone
18	M	Caucasian	60	N/A	N/A	N/A	N/A	Gamma interferon
19	M	Caucasian	47	2.9	55%	9.5	48%	Cyclophosphamide
20	M	Southeast Asian	63	2.34	60%	11.4	42%	Gamma interferon
21	M	Caucasian	65	1.54	48%	4.26	15%	Azathioprine

transplant was as follows: 1st year (9.8%), 2nd year (10.7%), 3rd year (10.4%) and 4th year (12.1%). On average the native lung volume declined by 9.5 cc/month. Using mixed model regression,[10] this was a statistically significant decline (95% CI: -12.67, -6.34, $p < 0001$). At the end of the 4 year period, the average patient had lost 29% of their total lung volume when compared to baseline (Fig. 4).

Immediately after transplant, 52% (range 7—100%) of the native lung was affected by fibrosis, compared to 65% at 2 years and 92% at 4 years. Excluding the 3 patients with chest CT scans with 100% of the lung affected by fibrosis, the average percentage of lung involved by fibrosis increased 11% per year for the 4 year period after transplant (Fig. 5). There was good agreement between the two readers with regards to the volume of lung affected by fibrosis using Pearson's correlation coefficient ($r = 0.9131$, $p < 0.001$).

All but five patients showed an overall $\geq$10% decrease in total lung volume during the study period. Of the five patients who showed <10% decrease in total lung volume one already had 100% of the lung affected by fibrosis, one had only 6 months of follow-up, and the other three showed an average increase of percent fibrosis of 31% over the 4 year post-transplant period.

Three patients had a native lung which was 100% affected by fibrosis and had CT follow-up for greater than 12 months. These patients showed an average decrease in total lung volume of 5.4%/year.

Abnormalities within the transplanted lung that showed increased attenuation, excluding mild scarring or atelectasis,

Table 2 Average total lung volume and % of lung affected by fibrosis in the native lung over time after single lung transplant.

Years after transplant	Lung volume (cc)	% Volume compared to baseline	% Lung affected by fibrosis	# Patients
0	1120	100%	52%	21
0.5	1091	97%	52%	21
1	1005	90%	59%	20
1.5	976	87%	62%	18
2	875	78%	65%	16
2.5	724	65%	72%	13
3	733	65%	78%	12
3.5	748	67%	76%	10
4	691	62%	92%	5

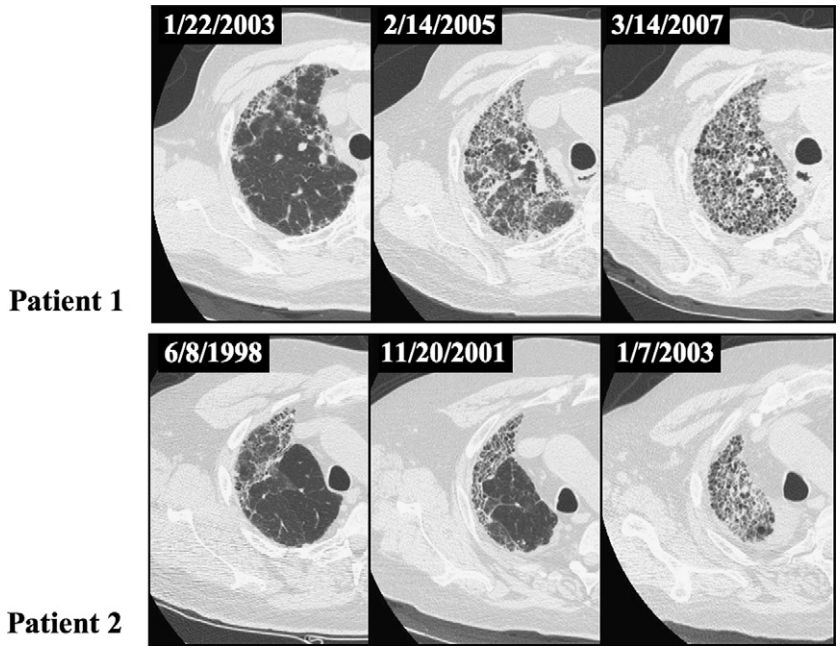

Figure 2 Progression of native lung fibrosis over time in 2 different IPF patients status post unilateral lung transplant. Over the 4—5 year intervals depicted in these patients there were significant decreases in lung volume and increase in percentage of lung affected by fibrosis.

were seen on a total of 24 of 136 CT scans. These abnormalities included the following: ground glass opacity (15), consolidation (4), extensive scarring (2), airways inflammation (2) and interlobular septal thickening (1). These abnormalities also involved the native lung in only two cases. In one of these cases the ground glass subsequently resolved, but in the other it was persistent and eventually evolved to fibrosis. It is possible this represented an acute exacerbation of IPF.

Mosaic perfusion and/or air trapping were seen on a total of 81 of 136 CT scans. This was classified as mild on 62 CTs, moderate on 14 CTs and severe on 5 CTs.

Discussion

IPF is a devastating disease with a very poor prognosis. Pharmacologic treatment of IPF has been largely ineffective and many clinical trials have been hampered by poor study design, making positive results of uncertain significance.[11] Traditional immunosuppression with steroids does not slow the progression of disease or incidence of acute exacerbations in the majority of patients.[1] Recent clinical trials have focused on immunomodulatory agents such as Interferon g-1b[12] and Pirfenidone.[13] In general, the use of these agents has shown only limited effectiveness in slowing the progression of IPF in specific patient subgroups.[14]

Single lung transplant patients with IPF at our institution are treated with a lifelong regimen of steroids, an antiproliferative agent (e.g. mycophenolate mofetil) and a calcineurin inhibitor (e.g. tacrolimus). The combination of these agents represents a significantly greater degree of immunosuppression than average treatment for non-transplanted patients with IPF. The primary goal of this study was to evaluate the ability of this combination of medications to arrest the progression of disease within the native lung. While mycophenolate has been suggested as a possible treatment for IPF,[15] to date there have been no clinical trials performed to assess the usefulness of either this drug or calcinuerin inhibitors in the treatment of IPF. There is one study which investigates the use of tacrolimus in attenuating drug induced fibrosis in a mouse model.[16]

In our study, the combination of medications used for lung transplant patients showed no ability to arrest the progression of fibrosis. There was a continued decline in lung volumes of 10.8%/year and increase in the percentage of lung affected by fibrosis of 11%/year for the four year period after transplant. There is little data quantifying the sequential progression of disease in patients with IPF prior to transplant. Most information has come out of short term follow-up in clinical trials. For instance, average decline of forced vital capacity over a 12 month period in the recent Bosentan trial ranged from 6.4 to 7.7%.[17] In a recent pirfenidone trial the decline in vital capacity over a 9 month period ranged from 0.03 to 0.13 L.[13] In our study the total native lung volume showed an average decline of 0.1 L/year for the first 4 years after transplant.

Virtually all patients showed either a decrease in native lung volume or an increase in the percentage of native lung affected by fibrosis in this study. There were two exceptions, one of which already had 100% of the lung affected by fibrosis and the other of which had only 6 months of follow-up. Thus, the combination of immunosuppressive agents used in this study did not arrest or even slow the progression of disease in the native lung over time.

To our knowledge, this is the first study to perform direct quantitative analysis of lung volumes and percentage of lung affected by fibrosis in single lung transplant patients with IPF over time. Two other studies have evaluated progression of lung fibrosis after transplant.[18,19] Our study involves a larger population group (21 vs. 5 and 13 patients

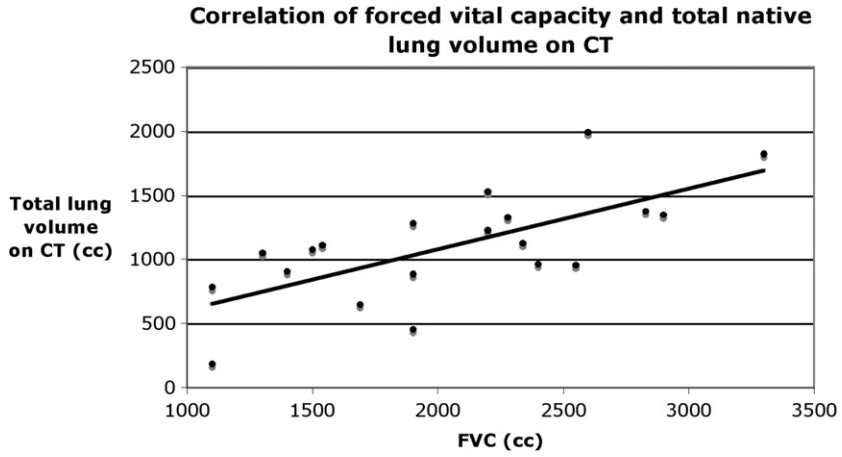

Figure 3 Forced vital capacity on PFTs immediately prior to transplant compared to total native lung volume calculated on CT immediately after transplant. Note that the FVC includes both lungs, however the total lung volume CT calculation is only for the one remaining lung. Trendline using linear regression analysis is shown.

respectively) and performed direct measurements of lung volumes and percentage of lung affected by fibrosis as opposed to using semi-quantitative measurements. The semi-quantitative method likely provides a less precise measurement of disease and is difficult to interpret in the context of pulmonary function measurements. While labor intensive, these quantitative measurements may in the near future may be very easy to calculate using automated computerized models, currently under development.[20] Additionally, the patients in the study by Grigic et al. received a cyclosporine-based regimen, whereas our patients were given the combination of an anti-proliferative agent and a calcineurin inhibitor. Our regimen arguably represents a greater degree of immunosuppression.

A few other studies have evaluated changes on serial CTs of non-transplanted IPF patients[21–23] who were either not treated with immunosuppressive agents or who were treated with traditional IPF agents. All have shown progression of CT findings in both groups.

There are several other interesting observations in this study. First, the lung volume and percentage of lung affected by fibrosis are widely variant in patients who have just been transplanted. The lung volumes range from 182 to 1994 cc and the percentage of lung affected by fibrosis ranges from 7 to 100%. This strongly suggests that the severity of fibrosis does not necessarily correlate with the need for transplant and that other significant factors contribute to a worsening clinical status. Pulmonary arterial hypertension is likely a significant contributor and does not always correlate with the severity of lung fibrosis either on CT[24] or as calculated on PFTs.[25] While hypoxic reflex vasoconstriction and perivascular fibrosis are significant contributors to pulmonary hypertension in chronic fibrotic lung diseases, other etiologies such as vascular inflammation and thrombosis also have been suggested to play a role.[26] This would explain discrepancies between severity of fibrosis and need for transplant.

The natural history of disease in the native lung beyond the point at which the patient would typically survive is not known. It is interesting to note that fibrosis in the native lung continues to progress at a rapid rate even with severe baseline disease. Lung volumes decrease even in some patient's whose lungs are entirely affected by fibrosis, suggesting worsening of the fibrosis on a microscopic level. Understanding the natural progression of disease within the native lung will also serve to prevent misinterpretation of

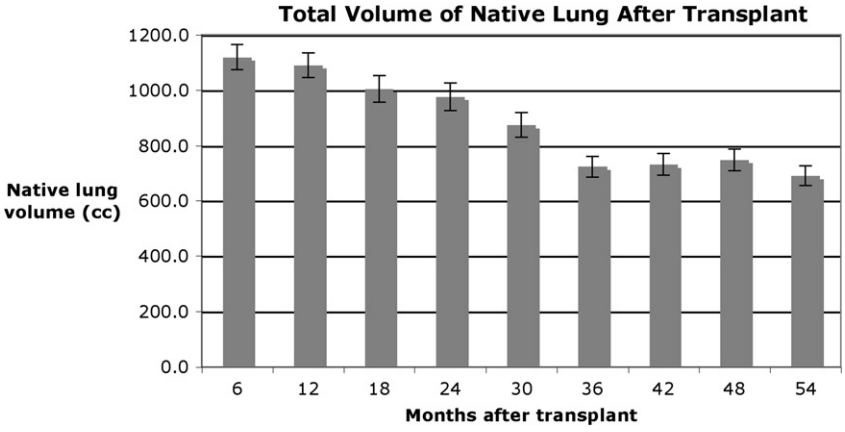

Figure 4 Plot of average volume of the native lung over time after single lung transplant. Standard error of measurement bars is provided.

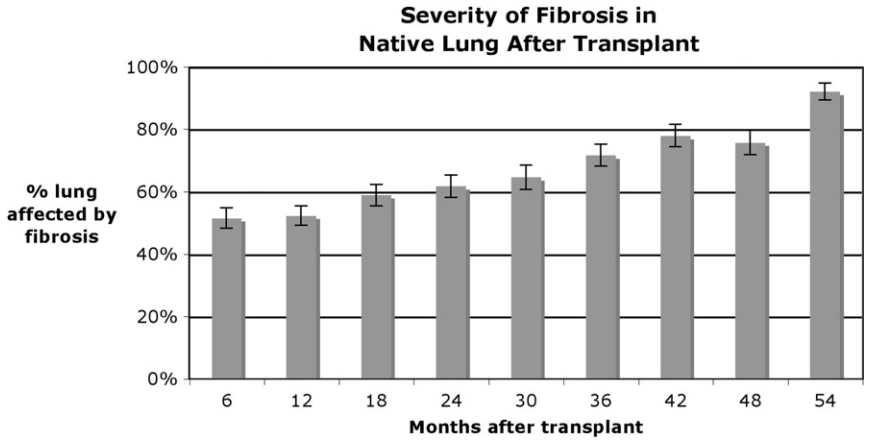

Figure 5 Plot of percentage of native lung affected by fibrosis over time after single lung transplant. Standard error of measurement bars is provided.

CT scan changes over time. As findings in fibrotic lung are characteristically difficult to interpret, progression of fibrosis should not be mistaken for infection or other entities that may produce increased lung opacity.

To our knowledge, there has been only one patient in our lung transplant practice that has been diagnosed with an acute exacerbation of IPF after single lung transplant. This patient was not transplanted during the study period. Upon review of the CT scans of the patients included in this analysis, one patient was identified with acute ground glass in the native lung which persisted and subsequently progressed to fibrosis. It is possible that this also represented an acute exacerbation. As acute exacerbations predominantly involve the fibrotic lung, it is rare to obtain definitive proof of disease in transplanted patients. Also, the incidence of acute exacerbation of IPF in the non-transplant IPF population is not clearly defined. Thus, we cannot make any conclusions about the ability of our immunosuppressive regime to decrease the incidence of acute exacerbation. It is interesting to note, however, that the ground glass opacity in this patient also affected the transplanted lung, albeit to a much lesser extent. It is possible that an acute exacerbation of IPF in single lung transplant could have some negative effects on not only the native lung, but the transplanted lung as well.

There are several potential limitations to this study. The HRCT technique, which only provides a sampling of the lung allows for slight inconsistencies from scan to scan. Validity of the calculation of lung volumes and percentage of lung affected by fibrosis assumes a relative homogeneity of disease between images taken at selected levels. While this may lead to slight inconsistencies over the short term, there was convincing long-term decrease in volume and increase in percentage of fibrotic lung over multiple follow-up scans. Another limitation is the relatively small number of patients included in analysis at the 4 year point (5). This is inevitable as the average national 3 year survival of lung transplant patients is approximately 60%.

In conclusion, the native lung in transplant patients with IPF continues to show a decrease in total lung volume and increase in the percentage of lung affected by fibrosis over time. This occurs despite a combination of potent immunosuppressive agents. It is known that steroids do not likely arrest the progression of disease in IPF. The other agents used in lung transplant patients, anti-proliferative agents (e.g. mycophenolate mofetil) and a calcineurin inhibitor (e.g. tacrolimus), also do not appear to arrest the progression of disease in IPF patients. These results have significant implications for future clinical trials involving these agents.

Conflict of interest

The authors have no conflict of interest to disclose.

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