Rates of change in FEV1 and *D*LCO as potential indicators for mTOR inhibitor therapy in premenopausal lymphangioleiomyomatosis patients

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ABSTRACT   The value of rates of change in forced expiratory volume in 1 s (FEV1) and diffusing capacity of the lung for carbon monoxide (*D*LCO) to predict disease progression, and initiation of mTOR (mechanistic target of rapamycin) inhibitor therapy has not been evaluated.

In 84 premenopausal lymphangioleiomyomatosis patients, individual rates of change in FEV1 and *D*LCO and their 95% confidence intervals were used to derive subsequent lowest values of FEV1 and *D*LCO that would prompt initiation of sirolimus therapy. These treatment criteria were compared with a criterion based on FEV1 or *D*LCO ⩽70% predicted. In 12 patients undergoing sirolimus therapy both methods for determining the optimal point for initiation of therapy were evaluated.

27 and 35 patients who experienced greater than expected rates of change in FEV1 and *D*LCO, respectively, would have been excluded from therapy based on an FEV1 or *D*LCO >70% pred. 25 of the 84 patients were eventually treated, but only when FEV1 or *D*LCO were ⩽70% pred. Applying such treatment criteria to 12 patients undergoing sirolimus therapy would have delayed treatment for many years.

Premenopausal females in whom FEV1 or *D*LCO are declining at rates above the expected based on their individual rates of decline, should be considered for sirolimus therapy before the FEV1 or *D*LCO falls to ⩽70% pred.

Introduction

Lymphangioleiomyomatosis (LAM) is a rare disease that affects females predominantly and involves the lungs, causing cystic destruction, recurrent pneumothoraces and dyspnoea; thoraco-abdominal and pelvic lymphatics, leading to lymphatic masses, i.e. lymphangioleiomyomas, and chylous effusions; and the kidneys, where it may present as mixed mesenchymal tumours named angiomyolipomas [1]. LAM may occur sporadically and in subjects with an autosomal dominant neurocutaneous disorder, tuberous sclerosis complex (TSC) [1].

LAM cells contain mutations in the TSC genes TSC1 and TSC2, which encode the proteins hamartin and tuberin, respectively [2–4], which exist as a cytosolic complex. Tuberin is a GTPase-activating protein for Ras homologue enriched in brain (Rheb) [5]. Loss of hamartin or tuberin activity causes accumulation of active Rheb–GTP and stimulation of its effector, mechanistic target of rapamycin (mTOR) complex 1, which results in increased cell size and proliferation [5]. This finding led to the concept that mTOR inhibitors, such as sirolimus, could be used to treat patients with LAM, and was followed by the Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus (MILES) double-blind controlled study of sirolimus in patients with LAM [6].

The MILES trial showed that sirolimus stabilises lung function in patients with forced expiratory volume in 1 s (FEV_1) $\leqslant$70% predicted [6]. Isolated reduction in diffusing capacity of the lung for carbon monoxide (D_{LCO}) $\leqslant$70% was not a criterion for enrolment. Accordingly, the MILES trial criteria for initiation of mTOR inhibitor therapy excluded patients with FEV_1 >70%, who, by the time their FEV_1 declined to $\leqslant$70% pred, might have lost one-third or more of their lung function.

Although there is general agreement that LAM patients with chylous effusions and lymphangioleiomyomas and angiomyolipomas benefit from mTOR inhibitor therapy [1], no criteria based on FEV_1 or D_{LCO} and their rates of decline have been proposed to identify LAM patients at risk for disease progression who may benefit from earlier initiation of mTOR inhibitor therapy, except those derived from the MILES trial. The problem with identifying such patients at an earlier date is that rates of decline of FEV_1 and D_{LCO} are variable [7–9]. JOHNSON and TATTERSFIELD [8] reported a mean±SD rate of FEV_1 decline of 118±142 mL·year^{-1} in 43 patients and a rate of D_{LCO} decline of 0.905±1.54 mL·min^{-1}·mmHg^{-1} in 33 patients. They noted that the greater the number of tests employed in deriving the slopes of FEV_1 and D_{LCO} per year, the less the variation between measurements. Another group [9] reported mean±SEM rates of FEV_1 decline of 75±9 mL (1.7±0.4% pred) and a reduction in D_{LCO} of 0.69±0.07 mL·min^{-1}·mmHg^{-1} (2.4±0.4% pred) per year. However, this study comprised post-menopausal patients and patients with LAM-TSC, who may have had milder lung disease [9]. Other studies reported higher rates of decline in FEV_1 in patients with reduced D_{LCO} [10], patients with FEV_1 $\leqslant$70% pred [11], patients presenting with dyspnoea instead of pneumothorax [12] and patients with a positive response to bronchodilators [13], suggesting that such patients may warrant earlier sirolimus therapy. Given these data, we questioned whether waiting to start mTOR inhibitor therapy until patients have experienced reductions in FEV_1 or D_{LCO} to $\leqslant$70% pred was a justifiable criterion for therapy.

Apart from the European Respiratory Society (ERS) [14] and American Thoracic Society (ATS)/Japanese Respiratory Society [15] consensus statements suggesting that sirolimus may be considered for patients with rapid decline in lung function, no guidelines for initiation of mTOR inhibitor therapy or enrolment in clinical trials based on accelerated loss of function have been established. Such a determination depends on whether a decline in FEV_1 or D_{LCO} corresponds to true progression of disease or is a random variation without clinical significance; several other factors such as the reproducibility of the test and the quality of the testing need to be considered.

Although LAM may have varying clinical courses and different factors may affect rates of disease progression, the aim of our study was to assess the value of past rates of functional decline in predicting future FEV_1 or D_{LCO} values to provide a method for potentially anticipating therapy with sirolimus prior to greater losses in lung function. We focused our research on premenopausal patients only and defined a rapid decline in FEV_1 or D_{LCO} as one that is greater than the greater 95% confidence interval for the individual rates of decline based on four tests performed within 18 months.

Accordingly, the aims of our study were to determine whether measurement of four or more FEV_1 or D_{LCO} performed over 18 months could predict future declines in lung function, which might prompt earlier initiation of mTOR inhibitor therapy. The rationale to evaluate in addition a treatment criteria based on rates of decline of D_{LCO} and a D_{LCO} $\leqslant$70% pred was prompted by those patients who have FEV_1 >70% pred, and experience persistent decline in D_{LCO}. Inasmuch as such patients were not the subject of the MILES trial, we thought that excluding LAM patients with reduced D_{LCO} from this analysis appeared to be inappropriate.

Materials and methods

Patient population

From a cohort of 173 patients participating in a LAM natural history and pathogenesis protocol (National Heart, Lung, and Blood Institute (NHLBI) protocol 95-H-0186), which was approved by the NHLBI institutional review board, we identified 84 premenopausal patients seen within a span of 5 years, who are the subject of this study. The demographic features of the 84 patients are shown in table 1. Patients were diagnosed with LAM based on clinical, radiographic and histopathological criteria (table 1) [14, 15]. 18 patients had TSC-LAM and the remaining 66 had sporadic LAM. 25 patients were eventually treated with sirolimus, but all data presented here were obtained before therapy.

To characterise the pattern of lung function decline in patients who eventually were begun on mTOR inhibitor therapy, we examined lung function data from a cohort of 118 LAM patients undergoing therapy with mTOR inhibitors. Among those patients, we identified 12 without evidence of lymphatic disease, who were started on sirolimus therapy because of an FEV_1 and/or D_{LCO} $\leqslant$70% pred and for whom lung function studies comprising many years of observation prior to therapy made possible the assessment of pre-therapy patterns of lung function decline. The aim of this component of our research was to determine how many years and what rates of decline were experienced prior to initiation of treatment based either on a FEV_1 $\leqslant$70% pred or a D_{LCO} $\leqslant$70% pred. This group of patients were tested every 6–12 months. Clinical, laboratory tests, chest radiographs and pulmonary function dataea were obtained at each visit. Exercise tests and imaging studies were obtained yearly and every 2 years, respectively. All FEV_1 values reported in the article refer to pre-bronchodilator data.

Pulmonary function testing

Lung volumes and flow rates were measured using a Master Screen PFT (Erich Jaeger, Wuerzburg, Germany) system according to ATS/ERS standards [16–18].

Study design

We estimated individual yearly rates of change of FEV_1 and D_{LCO} in 84 subjects seen within a time span of 5 years, who were tested at least five times, where the most recent test was within 18 months of the

TABLE 1 Demographic features of 84 premenopausal lymphangioleiomyomatosis (LAM) patients

Patients	84
Age at LAM diagnosis years	34.7±7.1
Age at first symptoms years	32.0±7.2
History of pneumothorax	48 (57)
History of TSC	18 (21)
History of chylothorax	19 (22)
History of lymphangioleiomyomas	26 (31)
History of angiomyolipoma	49 (58)
History of anti-oestrogen therapy	29 (34)
History of pneumonia	7 (8)
Initial presentation	
Dyspnoea	25 (30)
Pneumothorax	33 (39)
Haemoptysis	7 (8)
Abdominal pain	5 (6)
Cough	4 (5)
Chest pain	3 (3)
No symptoms	7 (8)
Mode of diagnosis	
Lung biopsy	43 (51)
Abdominal mass biopsy	6 (7)
Characteristic CT and TSC	10 (12)
Characteristic CT and lymphangioleiomyoma	8 (10)
Characteristic CT and angiomyolipoma	7 (8)
Characteristic CT and chylous effusion	1 (1)
Characteristic CT scan and elevated serum VEGF-D levels	2 (2)

Data are presented as n, mean±SD or n (%). TSC: tuberous sclerosis complex; CT: computed tomography; VEGF: vascular endothelial growth factor.

previous one (figure 1). The most recent visit was excluded from the derivation of the rates of change (slope) of FEV1 and D_{LCO}. The remaining visits were used to derive the slopes and 95% confidence interval for each subject [9]. Then, for each subject, we determined the expected lower values of FEV1 and D_{LCO} using their individual rates of change, the higher limit of the 95% confidence interval, the last measurement used in the derivation of slopes and the time elapsed from this visit until the next measurement of FEV1 and D_{LCO}.

Although the reproducibility of D_{LCO} measurements is considered to be less than that of FEV1, there are LAM patients in whom FEV1 is well preserved and D_{LCO} is reduced and declines progressively. We suggest that in these patients, a decline in D_{LCO} indicates progression of lung disease which may be confirmed by exercise testing that may uncover worsening exercise-induced hypoxaemia, and by quantitative computed tomography grading of cystic lung disease severity. We believe that patients with a FEV1 >70% pred and a declining D_{LCO} should be considered for sirolimus therapy.

We hypothesised that if the last actual FEV1 or D_{LCO} percentages measured were lower than the expected lower limit calculated from the individual rates of decline of FEV1 % pred or D_{LCO}% pred, treatment with mTOR inhibitors would be considered. That is, the calculated expected lower limit of FEV1 or D_{LCO} was compared to the last actual measurement not used in the derivation of slopes. If these values were lower than the expected, patients were considered to have rapid decline in function. These expected lower limits of FEV1 or D_{LCO} were taken to be a threshold below which treatment would be considered.

Three algorithms were used to assess whether treatment would be considered or not: 1) if the last actual FEV1 % pred was lower than its expected lower limit calculated above, treatment would be considered; 2) if the last D_{LCO} % pred value was lower than its expected lower limit calculated above, treatment would be considered; the criteria for treatment based on the above analytic methods were compared to 3) conventional treatment criteria based on FEV1 or D_{LCO} ⩽70% pred.

Results

Demographics
The mean±SD (range) age of the 84 premenopausal patients was 38.5±6.6 (19–46) years. Age of diagnosis and age of first LAM-related symptoms were 34.7±7.1 (18.7–45.5) years and 32.0±7.2 (16.7–44.2) years, respectively. Demographic features of these patients are shown in table 1. The mean±SD (range) age of the group of 12 patients who were eventually started on sirolimus was 37.8±9.4 (24–53) years at the time of the first visit, and 51.4±9.8 (35–68) years at the time of initiation of mTOR inhibitor therapy.

Indications for mTOR inhibitor therapy based on individual rates of change of FEV1 and D_{LCO} and their 95% confidence intervals
The 84 premenopausal patients underwent a total of 526 tests. All pulmonary function data were collected over a period of 5 years [8]. The mean±SEM (95% CI) yearly rate of change of FEV1 was −72±13 (−98–−46) mL
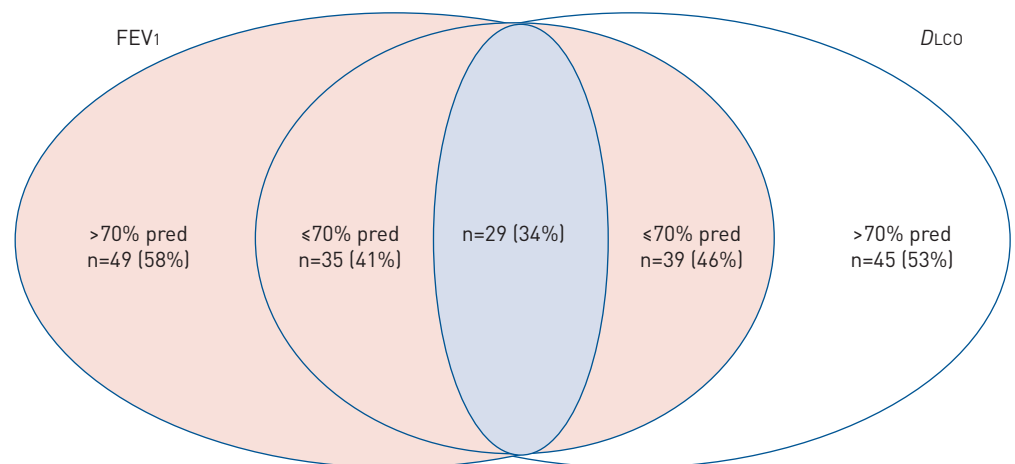

FIGURE 1 Venn diagram representing the forced expiratory volume in 1 s (FEV1) and diffusing capacity of the lung for carbon monoxide (D_{LCO}) profile of 84 premenopausal lymphangioleiomyomatosis (LAM) patients. Of the 84 patients, 49 had FEV1 >70% predicted and 45 had D_{LCO} >70% pred. 35 patients had FEV1 ⩽70% pred and 39 had D_{LCO} ⩽70% pred. 29 patients had both FEV1 and D_{LCO} ⩽70% pred. 12 out of the 49 patients with FEV1 >70% pred and 11 out of the 45 patients with D_{LCO} >70% pred had greater than expected declines in in FEV1 and D_{LCO}, respectively.

or -1.93 ± 0.46 (-2.84–-1.03)% pred. The mean±SEM yearly rate of change in D_{LCO} was -0.49 ± 0.11 (-0.70–-0.27) mL·min^{-1}·mmHg^{-1} or -1.97 ± 0.51 (-2.98–-1.03)% pred.

Among the 84 patients (table 2) we identified 27 (32.1%) with decline in FEV_1 and 35 (41.7%) with decline in D_{LCO} greater than expected. The mean±SEM (95% CI) rates of change in FEV_1 and D_{LCO} in 35 premenopausal patients with FEV_1 ⩽70% pred and 39 patients with D_{LCO} ⩽70% pred were -112 ± 19 (-151–-73) mL or -3.59 ± 0.67 (-4.91–-2.27)% pred, and -0.63 ± 0.14 (-0.91–-0.3) mL·min^{-1}·mmHg^{-1} or -2.75 ± 0.70 (-4.12–-1.38)% pred, respectively. Of these, 15 and 24, respectively, also met the FEV_1 ⩽70% and the D_{LCO} ⩽70% criteria for mTOR inhibitor therapy. However, 12 patients with decline in FEV_1 greater than expected, and 11 with a decline in D_{LCO} greater than expected would not have been treated if the criteria used for treatment was FEV_1 ⩽70% pred or a D_{LCO} ⩽70% pred.

The expected median (interquartile range (IQR)) time to get to a FEV_1 ⩽70% pred in subjects with FEV_1 decline greater than expected was 7.4 (4.0–13.4) years. For D_{LCO}, the expected median (IQR) time to get to a D_{LCO} ⩽70% pred in subjects with greater than expected decline was 13.6 (2.3–24.4) years. We used median instead of mean values, because the distribution is skewed.

In addition, we focused on how long it would take in patients with FEV_1 or D_{LCO} >70% pred for these functional parameters to be reduced to ⩽70% pred. We identified 16 patients with FEV_1 >70% pred who were followed for 8.3±4.5 years. FEV_1 was reduced from 87±13% pred to 68±2% pred (p<0.001) at an annual rate of 88±11 mL·year^{-1} or 2.4±0.3% pred·year^{-1} (online supplementary table S1). In 20 patients with D_{LCO} >70% pred followed for 7.4±4.8 years, D_{LCO} declined from 83±13% pred to 67±3% pred at an annual rate of 0.74±0.09 mL·min^{-1}·mmHg^{-1}, or 2.9±0.4% pred·year^{-1}. Of these patients, only eight and six were eventually treated with sirolimus, but not before FEV_1 or D_{LCO}, respectively, had fallen to ⩽70% pred.

Indications for mTOR inhibitor therapy based on individual rates of change in FEV_1 or D_{LCO} and their 95% confidence intervals in patients with FEV_1 or D_{LCO} >70% pred

The mean±SEM (95% CI) rates of change in FEV_1 and D_{LCO} in premenopausal patients with FEV_1 or D_{LCO} >70% pred were -63 ± 25 (-39–164) mL or -0.75 ± 0.58 (-1.94–0.44)% pred and -0.20 ± 0.11 (-0.66–0.26) mL·min^{-1}·mmHg^{-1} or -1.29 ± 0.74 (-2.75–0.18)% pred, respectively. Of this subgroup of patients (table 3), 12 (24.5%) had lower than the expected FEV_1, and 11 (24.4%) had lower than the expected D_{LCO} (table 3). Two of the 23 patients had greater than expected rates of decline in FEV_1 and D_{LCO}. The remaining patients had a decline in at least one of the two criteria.

Time course and rates of change in FEV_1 and D_{LCO} preceding therapy in 12 LAM patients treated with mTOR inhibitors

Initial mean±SD FEV_1 and D_{LCO} were 2.8±0.5 L (97±10% pred) and 20.6±3.9 mL·min^{-1}·mmHg^{-1} (89.1±11.5% pred), respectively (table 4). We measured the rates of change of FEV_1 and D_{LCO} using four tests and compared FEV_1 and D_{LCO} values from the fourth test with values from tests performed 9.8±4.1 months later. We found that during this period of time FEV_1 and D_{LCO} changed by −3.3% pred

TABLE 2 Comparator analysis of treatment of 84 premenopausal lymphangioleiomyomatosis patients based on lung function criteria *versus* an analytical method derived from individual rates of functional decline and confidence intervals

	Treated based on analytical method?		
	Yes	**No**	**Total**
FEV_1 ⩽70% pred			
Yes	15 (17.9)	20 (23.8)	35 (41.7)
No	12 (14.3)	37 (44.0)	49 (58.3)
Total	27 (32.1)	57 (67.9)	84 (100)
D_{LCO} ⩽70% pred			
Yes	24 (28.6)	15 (17.9)	39 (46.4)
No	11 (13.1)	34 (40.5)	45 (53.6)
Total	35 (41.7)	49 (58.3)	84 (100)

Data are presented as n (%). Rows show the number of patients who would be treated with mechanistic target of rapamycin (mTOR) inhibitors if forced expiratory volume in 1 s (FEV_1) ⩽70% predicted or diffusing capacity of the lung for carbon monoxide (D_{LCO}) ⩽70% pred. Columns show the number of patients to be treated with mTOR inhibitors when the observed FEV_1 or D_{LCO} was lower than the expected values derived from rates of decline in FEV_1 and D_{LCO}.

TABLE 3 Analysis of potential treatment of lymphangioleiomyomatosis patients based on a method derived from rates of decline in premenopausal patients with forced expiratory volume in 1 s (FEV1) or diffusing capacity of the lung for carbon monoxide (D_{LCO}) >70% predicted

	Treated based on analytical method		
	Yes	No	Total
FEV1 >70%	12 (24.5)	37 (75.5)	49 (100.0)
D_{LCO} >70%	11 (24.4)	34 (75.6)	45 (100.0)

Data are presented as n (%). Columns show the numbers of patients to be treated with mTOR (mechanistic target of rapamycin) inhibitors when the observed FEV1 and D_{LCO} were lower than the expected values derived from rates of decline in FEV1 and D_{LCO}.

and −5.3% pred, respectively and FEV1 and D_{LCO} values were significantly lower than those observed on the last test utilised to estimate the rates of change (table 4). By the time the patients were begun on therapy, FEV1 and D_{LCO} had declined even further, to 1.7±0.4 L (68.4±19.2% pred) and 12.4±2.8 mL·min^{-1}·mmHg^{-1} (60.8±11.8% pred), respectively.

Discussion

This is the first study where an analysis of rates of decline in FEV1 and D_{LCO} predicts greater loss of function before patients cross the 70% pred FEV1 threshold, which, based on the MILES study, became an accepted standard for initiation of sirolimus therapy. In the current study we show that in 84 premenopausal LAM patients, using individual rates of functional decline in FEV1 or D_{LCO}, and 95% confidence intervals, an analytical method using estimated expected FEV1 % pred or D_{LCO} % pred based on past rates of FEV1 or D_{LCO} decline identifies patients with faster loss of lung function who had not yet crossed a therapeutic threshold of FEV1 or D_{LCO} ≤70% pred. These patients are at risk of experiencing a progressive loss of function before being considered for therapy.

Currently, mTOR inhibitor therapy may be recommended for subjects with lymphatic disease, and size of, or bleeding from angiomyolipomas, and those patients who have FEV1 ≤70% pred, based on the MILES study enrolment criteria. Two consensus statements have suggested that subjects with rapid disease progression should be considered for therapy, but rapid progression of disease was not defined [14, 15].

In our study we found that 23 of 49 premenopausal patients with FEV1 or D_{LCO} >70% pred experienced changes in FEV1 or D_{LCO} greater than the higher 95% confidence interval. These data suggest that some premenopausal LAM patients with FEV1 or D_{LCO} >70% pred may experience declines in lung function

TABLE 4 Lung function tests on first visit, at the time of estimation of rates of forced expiratory volume in 1 s (FEV1) and diffusing capacity of the lung for carbon monoxide (D_{LCO}) declines, the next test, and before and after sirolimus therapy in 12 patients with lymphangioleiomyomatosis

	First test	Last slope test	Next test	Pre-sirolimus	Post-sirolimus
Age years	35.6±9.4	41.2±9.3	42.0±9.2	49.4±9.6	53.3±10.3
TLC L	5.1±0.5	5.2±0.7	5.2±0.6	5.2±0.8	4.6±0.8
TLC % pred	100.6±9.1	101.5±11.2	100.8±10.3	105.2±17.4	93.0±12.3
FVC L	3.6±0.6	3.6±0.4	3.5±0.5	3.1±0.7	3.0±0.6
FVC % pred	100.8±13.7	104±12.3	101.4±13.8	89.3±36	94±15.1
FEV1 L	2.8±0.44	2.45±0.23	2.28±0.28	1.72±0.48	1.62±0.4
FEV1 % pred	97±10.1	90.2±11.1	85±13	68.4±19.2	67.6±17.9
D_{LCO} mL·min^{-1}·mmHg^{-1}	20.6±3.9	16.45±2.3	15.1±1.9	12.4±2.8	11.2±3.4
D_{LCO} % pred	89.1±11.5	77.6±7.9	71.6±7	60.8±11.8	56.5±14.7
Change in FEV1 mL·year^{-1}				−105±17	−40±24
Change in FEV1 % per year		−3.7±1.3	−3.3	−3.0±0.5	−1±0.8
Change in D_{LCO} mL·min^{-1}·mmHg^{-1}·year^{-1}				−0.66±0.06	−0.05±0.14[#]
Change in D_{LCO} % per year		−2.6±1.5	−5.3	−2.6±0.3	0.02±0.6[#]
Time since first test years		5.9±2.8	6.7±2.8	14.1±4.6	18.0±4.8

Data are presented as mean±SD. Rates of decline are expressed as means±SEM. TLC: total lung capacity; FVC: forced vital capacity. [#]: p=0.001.

that will cause reductions in FEV_1 or D_{LCO} to ⩽70% pred in a given time. Our data suggest that such patients should undergo frequent lung function testing to calculate rates of decline of FEV_1 and D_{LCO} over time. Subsequent testing will determine whether FEV_1 or D_{LCO} values are lower than the expected values derived from the lower limit of the 95% confidence interval.

However, it should be noted that it has not yet been established whether a patient whose lung function is falling but still has an FEV_1 or D_{LCO} >70% pred should receive mTOR inhibitor therapy. Our data suggest that at a minimum, these patients are at additional risk of progression of lung disease and warrant close follow-up with frequent monitoring of disease by lung function testing and estimation of rates of FEV_1 and D_{LCO} decline. In the case of D_{LCO}, disease progression may be confirmed by other means such as new onset of exercise-induced hypoxaemia or quantitative grading of lung disease using computed tomography, which, if confirmed may further ascertain the need for initiation of therapy. The alternative to this approach, waiting to initiate of mTOR inhibitor therapy until either FEV_1 or D_{LCO} have fallen to ⩽70% pred may result in greater loss in lung function. This was confirmed by data from 12 patients who were begun on sirolimus therapy eventually, because of reductions in FEV_1 and/or D_{LCO} from values ⩾80% pred to values ⩽70% pred (table 4). Indeed, after measuring rates of decline in lung function employing four tests, we found that a fifth test performed within a year showed further losses in lung function. Treatment with mTOR inhibitors should have been started at that point instead of much later, when patients had already lost >20% of the FEV_1 and >15% of the D_{LCO} (table 4). We suggest that a case can be made for initiation of therapy for those patients in whom tests performed after estimating the rate of decline in function demonstrate persistent large declines in FEV_1 or D_{LCO}. Such decisions must be balanced against the risks of drug toxicity. Perhaps low-dose sirolimus therapy could be considered in patients who have not yet reached the 70% pred FEV_1 or D_{LCO} threshold [19].

We compared using the individual 95% confidence of rates of change in FEV_1 or D_{LCO} with the confidence interval for the entire group mean rates of decline in FEV_1 or D_{LCO}. Fewer patients who would be potential candidates for mTOR inhibitor therapy were identified when individual rates of decline were employed. Indeed, the analysis based on group rates performed better than one based on individual rates and 95% confidence limits. However, similar data from relatively large LAM patient populations are not available to practising physicians. Therefore, we suggest using individual rates and a minimum of four tests within a period of 18 months to estimate the changes in FEV_1 and D_{LCO}. If subsequent testing yields FEV_1 or D_{LCO} values lower than the expected lower limit, and in absence of an obvious cause for this change such as a recent pneumothorax, pleurodesis or intercurrent respiratory infection, initiation of mTOR inhibitor therapy should strongly be considered.

In our experience, the reproducibility of FEV_1 measurements in LAM patients is generally good, but occasionally a patient may experience differences that may reach 7–8% between two measurements (online supplementary figure S1). In the case of D_{LCO} the problem is more complex, because of the greater intra-individual variability of this test [17]. In this case, exercise testing and imaging studies may assist in determining whether a measured reduction in D_{LCO} parallels new onset of exercise-induced hypoxaemia or increase in lung cysts.

A major concern with this approach is the timing of initiation of therapy in patients in whom lung function is declining at a steady, yet slow, rate. Let us take a patient in whom FEV_1 or D_{LCO} declines every year, but at a slow rate of 1–2% per year. Should treatment be started when their values reach <80% pred? In addition, it remains to be defined whether earlier initiation of mTOR inhibitors, including in those with normal FEV_1 and D_{LCO} or FEV_1 or D_{LCO} >100% pred, would be beneficial for patients with LAM. However, we suggest that evaluation of the rate of change in FEV_1 and D_{LCO} may have a special importance in those patients in whom values of FEV_1 or D_{LCO} are >100% pred. In this population, to wait until FEV_1 and D_{LCO} reach 70% pred to initiate the use of sirolimus would be more deleterious because it results in a 30% loss of lung function. Measurement of cyst scores using computed tomography may help defining progression of disease [20]. At present, definite answers to these questions cannot be provided.

Based on our data, we recommend that premenopausal LAM patients in whom lung function is declining steadily at rates well above the expected, based on their estimated rates of decline, should be followed closely and be strongly considered for mTOR inhibitor therapy before the FEV_1 or D_{LCO} falls to ⩽70% pred.

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