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Long-term outcomes of sirolimus therapy in sporadic and tuberous sclerosis complex–associated lymphangioleiomyomatosis: a retrospective cohort study

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Abstract

Introduction Sirolimus is the standard disease-modifying therapy for lymphangioleiomyomatosis (LAM), but long-term routine-care data integrating pulmonary, lymphatic, extrapulmonary, and biomarker outcomes remain limited.

Objectives To assess long-term effectiveness and safety of sirolimus in routine clinical practice.

Patients and methods We retrospectively analyzed consecutive adults with definite LAM treated with sirolimus at a national tertiary referral center in Poland between 2010 and 2020.

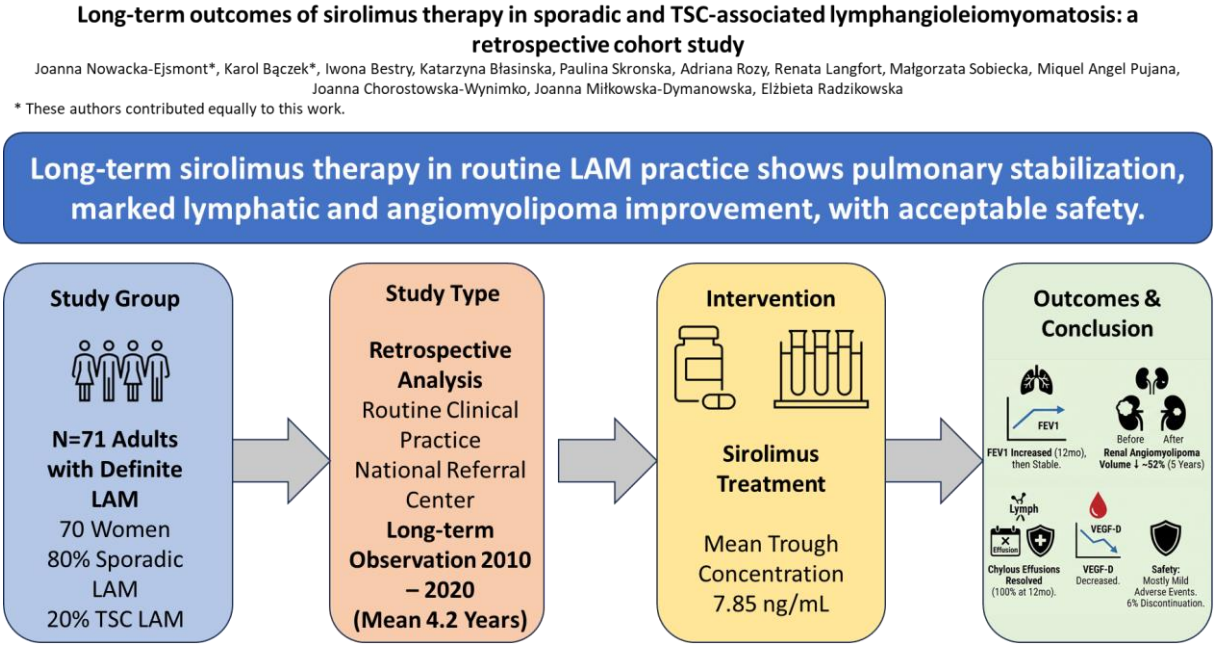
Results Seventy-one patients were included (70 women; 57/71 [80%] with sporadic LAM and 14/71 [20%] with TSC-associated disease). The median duration of available functional follow-up was 5.0 years [IQR, 2.0–5.0], and mean trough sirolimus concentration was 7.85 (2.36) ng/mL. Baseline chylous pleural and/or peritoneal effusions were present in 15/71 (21%), renal angiomyolipomas in 33/71 (46%), and lymphangioleiomyomas in 28/71 (39%) patients. FEV1 increased at 12 months by a median Δ of 0.03 L [IQR, −0.10 to 0.30] from baseline (n=66; P=0.03). FVC and 6-minute walk distance also improved during early follow-up, while TLCO remained generally stable. Chylous effusions resolved in all affected patients by 12 months without recurrence, and renal angiomyolipoma and lymphangioleiomyoma volumes decreased significantly in patients with paired MRI measurements. Higher baseline VEGF-D was associated with lymphatic involvement, and VEGF-D decreased during treatment. Adverse events were mostly mild; permanent discontinuation occurred in approximately 6%.

Conclusions In routine practice, sirolimus was associated with long-term stabilization of lung function, marked improvement of lymphatic disease, reduction of angiomyolipoma

burden, and acceptable tolerability. VEGF-D aligned with lymphatic phenotype and declined with treatment, supporting its role as a monitoring biomarker.

Key words:

lymphangioleiomyomatosis, mechanistic target of rapamycin, pulmonary function, sirolimus, VEGF-D



Introduction

Lymphangioleiomyomatosis (LAM) is a rare, progressive lung disease that predominantly affects women of childbearing age and is characterized by proliferation of abnormal smooth muscle-like LAM cells, which results in diffuse lung cyst formation. LAM occurs either as sporadic LAM (sLAM) or in association with tuberous sclerosis complex (TSC-LAM) [1]. It is driven by dysregulation of the mechanistic target of rapamycin (mTOR) pathway due to pathogenic variants in TSC1 or TSC2 [2–4].

Patients typically present with exertional dyspnea, cough, recurrent pneumothorax and chylous pleural and peritoneal collections. High-resolution computed tomography (HRCT)

demonstrates diffuse, thin-walled cysts with an even distribution in both lungs [5]. Extrapulmonary disease commonly includes renal angiomyolipomas (AMLs), retroperitoneal and, less frequently, mediastinal lymphangioleiomyomas, chylothorax and chyloperitoneum. Elevated serum vascular endothelial growth factor-D (VEGF-D) supports non-invasive diagnosis in the appropriate clinical and radiological context and correlates with lymphatic involvement and disease phenotype [2,3,6–11].

Pharmacological inhibition of mTOR is the current disease-modifying strategy in LAM. Randomized and prospective evidence has shown that sirolimus stabilizes lung function during active treatment and is associated with reductions in VEGF-D and improvement of selected clinical outcomes; after discontinuation, lung function decline may resume. International guidelines recommend sirolimus in patients with abnormal or declining lung function and in selected extrapulmonary manifestations, including clinically significant chylous effusions and AMLs [2,3,11–13].

However, long-term real-world data remain necessary to characterize durability of functional stabilization, safety in routine practice, extrapulmonary responses, and biomarker dynamics across heterogeneous phenotypes. In this retrospective unselected cohort study from a national tertiary referral center, we assessed long-term results of sirolimus therapy in LAM, focusing on pulmonary function (FEV1 - forced expiratory volume in 1 second, FVC - forced vital capacity, TLCO - transfer factor of the lung for carbon monoxide), exercise capacity (6MWT - 6-minute walk test), VEGF-D trajectories, and extrapulmonary manifestations including AML and lymphatic involvement. In addition, we explored correlations between sirolimus trough concentration and clinical outcomes and adverse events.

Patients and methods

Study design and population This retrospective cohort study included adult patients with definite LAM treated with sirolimus at a national tertiary referral center in Poland. All consecutive patients with definite sLAM and TSC-LAM who initiated sirolimus therapy during 2010–2020 were screened and analyzed as a historical routine-care cohort. This predefined time frame was selected to ensure a homogeneous treatment-initiation period and sufficiently long follow-up, while allowing detailed analysis of a large real-world dataset across pulmonary, lymphatic, extrapulmonary, and biomarker domains. Definite LAM was diagnosed according to ATS/JRS criteria [2]; in TSC-LAM, standard TSC diagnostic criteria were applied [14]. The analysis included 70 women and 1 man, all Caucasian, who received sirolimus and had pulmonary function tests at treatment initiation and at least 1 follow-up pulmonary function assessment. All treated patients were retained for descriptive summaries. Analyses were performed on an available-case basis.

Clinical and radiological assessment Clinical data were retrieved from medical records and dedicated LAM databases. Lymphatic involvement was defined as chylous pleural effusion, chylous ascites, and/or lymphangioleiomyomas on imaging (retroperitoneal or mediastinal). Renal AMLs were documented by ultrasound, CT (Computer Tomography), MRI (Magnetic Resonance Imaging) or histopathology; chylous nature of pleural or peritoneal fluid was confirmed biochemically whenever possible. HRCT assessed pulmonary lesions. Response of AMLs and lymphangioleiomyomas during sirolimus therapy was based on MRI and interpreted by an experienced radiologist (KB). For extrapulmonary manifestations, renal angiomyolipomas and lymphatic involvement, including chylous pleural/peritoneal effusions and lymphangioleiomyomas, were analyzed as binary variables. MRI-based volumetric measurements of angiomyolipomas and lymphangioleiomyomas were analyzed as secondary longitudinal outcomes.

Pulmonary function tests and exercise capacity PFTs were performed in accordance with ERS/ATS recommendations [15–17] at baseline (t0, sirolimus initiation), 3 months, 12 months, 24 months and then approximately every 2–3 years. FEV1, FVC and TLCO were extracted; lung volumes (TLC, RV) were collected when available. Exercise capacity was assessed by the 6MWT according to ATS guidance [18]; walked distance and SpO2 were recorded. Desaturation was defined as end-test SpO2 minus pre-test SpO2 [19].

Biomarkers Serum VEGF-D was measured at baseline (VEGF-D1) and, when available, closest to 12 months after sirolimus initiation (VEGF-D2), with additional measurements analyzed descriptively. VEGF-D was determined by enzyme-linked immunosorbent assay in duplicate, using the same laboratory methodology as in our previous studies on serum VEGF-D in cystic lung diseases and LAM. VEGF-D was analyzed as continuous (log-transformed when skewed) and categorized using thresholds (<600 pg/mL, 600–799 pg/mL, and ≥800 pg/mL).

Sirolimus treatment and safety Sirolimus was initiated at 2 mg/day and adjusted according to tolerability and trough serum concentrations (between 5-15ng/mL). Mean trough concentration per patient was defined as the arithmetic mean of all available trough measurements. Adverse events potentially related to sirolimus were extracted from a dedicated safety spreadsheet, grouped into clinically meaningful classes, and graded according to CTCAE version 5.0 [20]. Concomitant non-LAM medications were not captured in a fully standardized manner in the retrospective dataset and were therefore not analyzed quantitatively.

Exploratory phenotyping and response definitions Individual long-term slopes were estimated for FEV1 and TLCO only in patients with at least three available measurements for a given outcome. Slope-based categorical change was defined using prespecified annual change thresholds: improvement or deterioration was defined as a slope of at least +0.10 or

−0.10 L/year for FEV1 and at least +0.20 or −0.20 units/year for TLCO, respectively; values between these thresholds were classified as stable.

Threshold-based categorical change from baseline was assessed separately using absolute change from baseline. For FEV1 and FVC, a change of at least 150 mL was considered clinically relevant; for TLCO % predicted, a change greater than 10 percentage points was considered clinically relevant. These analyses were performed on an available-case basis in patients with paired baseline and follow-up data.

Statistical analysis Continuous variables are presented as mean (SD) when approximately normally distributed and as median [IQR] otherwise. Normality was assessed using the Shapiro-Wilk test and visual inspection of distributions. Categorical variables are presented as n (%). Between-group comparisons used Student's t test or Mann-Whitney U test for continuous variables, as appropriate, and χ^2 test or Fisher's exact test for categorical variables. Changes from baseline were assessed using paired t tests or Wilcoxon signed-rank tests in patients with available paired baseline and follow-up measurements. Results of repeated-measures analyses are presented as change from baseline, together with the number of paired observations for each comparison.

Correlations were assessed using Spearman's rank correlation coefficient and reported as Spearman's R.

Individual long-term slopes were estimated using patient-level linear regression of the measured value on time since sirolimus initiation, expressed in years. Slopes were calculated only for patients with at least three available measurements for a given outcome.

Exploratory multivariable logistic regression models were used to assess factors associated with lymphatic involvement and angiomyolipoma presence. Because of the limited sample size and low number of outcome events, the number of predictors was restricted. Candidate variables were selected a priori based on clinical relevance and biological plausibility. VEGF-

D was log-transformed because of skewed distribution. Results are presented as odds ratios with 95% confidence intervals.

Exploratory multivariable linear regression was used to assess predictors of change in FEV1 from baseline to 12 months. Independent variables were selected a priori and limited to clinically relevant predictors to reduce the risk of model overfitting. Regression assumptions were assessed by inspection of residual plots, normality of residuals, homoscedasticity, and influential observations. Results are presented as regression coefficients with 95% confidence intervals.

Given multiple outcomes and time points, analyses were exploratory and P-values were not adjusted for multiple comparisons. All tests were two-sided.

Results

Study population Seventy-one patients had definite LAM: 57/71 (80%) sLAM and 14/71 (20%) TSC-LAM; 70/71 (99%) were women. Patients with sLAM were older at diagnosis and at sirolimus initiation and had lower baseline lung function (notably FEV1 and TLCO) than patients with TSC-LAM; baseline 6MWD and VEGF-D were similar (Table 1). Among clinically relevant comorbidities, asthma was present in 29/71 (40.8%) patients and arterial hypertension in 28/71 (39.4%); overweight status was recorded in 3/71 (4.2%) patients, which is consistent with the distinctive clinical profile of this LAM cohort. Full comorbidity data are presented in Supplementary material, *Table S1*.

Sirolimus exposure The median duration of available functional follow-up was 5.0 years [IQR, 2.0–5.0], with a range of 0.25–8.0 years. Mean trough sirolimus concentration was 7.85 (2.36) ng/mL, range 3.5–14.0 ng/mL. Mean daily dose was stable early after initiation. All patients remained alive during long-term follow-up, with the exception of 1 patient who died during the early COVID-19 period. Longitudinal analyses were performed on an available-

case basis, and the number of evaluable patients varied across time points and outcome domains.

Lung function and exercise capacity In paired available-case analyses, FVC increased from baseline at 3 months (median Δ 0.11 L [IQR, 0.00 to 0.30]; n=65; P<0.001), 1 year (median Δ 0.11 L [IQR, −0.07 to 0.37]; n=67; P<0.001), and 2 years (median Δ 0.11 L [IQR, −0.11 to 0.31]; n=51; P=0.04), with no significant change at 5 years (median Δ 0.02 L [IQR, −0.36 to 0.29]; n=42; P=0.75).

FEV1 increased from baseline at 3 months (median Δ 0.10 L [IQR, 0.00 to 0.31]; n=62; P<0.001) and 1 year (median Δ 0.03 L [IQR, −0.10 to 0.30]; n=66; P=0.03), with no significant change at 2 years or 5 years.

The 6-minute walk distance increased at 3 months (median Δ 30 m [IQR, 0 to 50]; n=65; P<0.001), 1 year (median Δ 30 m [IQR, 0 to 76]; n=63; P<0.001), and 2 years (median Δ 30 m [IQR, 0 to 68]; n=50; P<0.001), while the 5-year change was not statistically significant. Subgroup analyses by baseline chylous effusion status are presented in Table 3 (with chylous effusion) and Supplementary material, *Table S2* (without chylous effusion).

Pneumothorax At sirolimus initiation, 27/71 (38%) had a history of pneumothorax, more frequent in sporadic than TSC-LAM (25/57 [44%] vs 2/14 [14%], P=0.06). During sirolimus, pneumothorax occurred in 5/71 (7%) patients, all with previous pneumothorax. Trough concentrations were lower in those with pneumothorax during therapy (median 5.8 [5.5–6.5] vs 7.8 [6.6–9.45] ng/mL; P=0.048); baseline VEGF-D did not differ (P=0.31).

Extrathoracic and lymphatic manifestations Among patients with paired MRI measurements, angiomyolipoma volume decreased significantly during sirolimus therapy. Median AML volume decreased from 98 to 77 cm^3 at 3 months (n=23; median Δ −13 cm^3; P=0.001) and from 69 to 60 cm^3 at 5 years (n=14; median Δ −7 cm^3; P=0.005).

Lymphangioleiomyoma volume also decreased significantly. Median lymphangioleiomyoma volume decreased from 157 to 65 cm^3 at 3 months (n=25; median Δ −52 cm^3; P<0.001) and from 167 to 0 cm^3 at 5 years (n=15; median Δ −113 cm^3; P<0.001). Chylous pleural and peritoneal effusions resolved in all affected patients by 12 months without recurrence.

VEGF-D and phenotype Baseline VEGF-D median was 1648 pg/mL (875–2992). VEGF-D strata were <600 pg/mL in 6/71 (8%), 600–799 pg/mL in 9/71 (13%), and ≥800 pg/mL in 56/71 (79%). Lymphatic involvement was more common in the ≥800 pg/mL group than in <800 pg/mL (30/56 [54%] vs 2/15 [13%], P=0.02). Pneumothorax prevalence did not differ by strata and AML prevalence was similar. VEGF-D decreased under sirolimus at follow-up (all paired comparisons vs baseline p<0.001). Higher baseline VEGF-D was associated with larger early reduction (Spearman R=−0.76, p<0.001). Correlations with functional parameters are provided in Supplementary material, *Table S3*. Baseline VEGF-D correlated with chylous effusion (Spearman R=0.45; P<0.001) and lymphatic involvement (Spearman R=0.42; P<0.001) (Table 4).

Severity strata based on baseline FEV1 Among patients with baseline FEV1% predicted, 35/70 (50%) had FEV1 <70% predicted and 35/70 (50%) had FEV1 ≥70% predicted. The <70% group had lower baseline FVC and TLCO% predicted, shorter 6MWD, and more frequent sLAM. Over 12 months, changes in FEV1, TLCO% predicted, and 6MWD improved in both strata; between-strata differences were not significant.

Long-term slopes and categorical change Individual slopes could be estimated in patients with at least three available measurements: 67/71 (94%) for FEV1 and 63/71 (89%) for TLCO. Median FEV1 slope was −0.008 L/year [IQR −0.063 to +0.040]. Using a threshold of ±0.10 L/year, 13/67 (19%) patients improved, 43/67 (64%) remained stable, and 11/67 (16%) deteriorated.

Median TLCO slope was −0.033 units/year [IQR −0.125 to +0.107]. Using a threshold of ±0.20 units/year, 13/63 (21%) patients improved, 39/63 (62%) remained stable, and 11/63 (17%) deteriorated.

Threshold-based categorical change from baseline was assessed separately in patients with paired follow-up measurements and is presented in the Supplementary Methods.

Exploratory multivariable models In logistic regression for lymphatic involvement, higher log-transformed baseline VEGF-D was independently associated with lymphatic disease (OR 5.20, 95% CI 2.04–13.21; P<0.001), while TSC-LAM was associated with lower odds compared with sLAM (OR 0.11, 95% CI 0.02–0.62; P=0.01). In a model for AML presence, TSC-LAM was an independent predictor (OR 5.83, 95% CI 1.46–23.27; P=0.01). In exploratory linear regression for ΔFEV1 from baseline to 12 months, the model explained 17% of variance (R^2=0.17). Lower baseline FEV1 was associated with greater 12-month improvement in FEV1 (β=−0.176 L per 1-L higher baseline FEV1; 95% CI −0.341 to −0.012; P=0.04), and younger age was also associated with greater improvement (β=−0.018 L per year; 95% CI −0.029 to −0.007; P=0.002). Disease type, lymphatic involvement, and baseline log-transformed VEGF-D were not independently associated with ΔFEV1.

Adverse events Adverse events occurred in all treated patients and were mainly mild, most commonly CTCAE grade 1. At 3 months, skin changes were recorded in 11/71 (15%) and oral mucosal symptoms in 4/71 (6%); 1 patient developed grade 3 mucosal toxicity requiring temporary interruption and subsequent dose reduction. Metabolic adverse events were frequent. Hypercholesterolemia, graded according to CTCAE laboratory thresholds, occurred in 16/71 (22%) at 3 months and in 11 patients at 5 years; broader lipid abnormalities were recorded in 13/71 (18%) at 3 months and in 5 patients at 5 years. Grade 3 hypercholesterolemia / hyperlipidemia occurred in 1 patient with mixed familial hyperlipidemia. Infections were common but usually mild. Nontuberculous mycobacteria

occurred in 2 patients and led to sirolimus discontinuation during antimycobacterial therapy; after discontinuation, LAM progression required home oxygen therapy in 1 of them, and the other additionally developed aspergilloma. Menstrual disturbances, used here as an umbrella term for menstrual irregularities documented in the medical records, were reported in 12 patients at 3 months and in 7 at 5 years. Other adverse events included headaches, dyspeptic symptoms, and lymphatic edema. Proteinuria was observed in 2 patients with TSC-LAM and very large angiomyolipomas. Permanent discontinuation due to adverse events occurred in approximately 6%, including 3 patients with abdominal discomfort in the setting of intestinal disease and 1 with a suspected sirolimus-related hypersensitivity reaction. In exploratory analyses, higher mean trough concentration at 3 months was associated with mucosal adverse events, and at 5 years lipid abnormalities were associated with mean trough concentration.

Discussion

This study adds long-term real-world data on sirolimus treatment in a national tertiary referral cohort of patients with LAM, integrating pulmonary trajectories with detailed lymphatic, extrapulmonary, biomarker, and exposure-related outcomes. Beyond overall stabilization of lung function during prolonged routine-care treatment, we observed complete resolution of chylous pleural and/or peritoneal effusions in all affected patients, sustained regression of angiomyolipoma and lymphangioleiomyoma volume, and a substantial decline in VEGF-D during therapy. The cohort also allowed parallel assessment of sporadic and TSC-associated disease and exploratory analysis of trough exposure in relation to pneumothorax and toxicity, supporting individualized long-term management.

The pulmonary outcomes in our cohort align with prior interventional and observational evidence showing that mTOR inhibition can halt or slow functional decline in LAM. In the randomized MILES trial, sirolimus stabilized lung function during the treatment phase, with

loss of benefit after discontinuation [12]. Observational studies similarly report stabilization of FEV1 and variable improvement across individuals [23–33]. In a prospective UK cohort, sirolimus improved FEV1 slope in patients with available pre-treatment trajectories, while inter-individual variability remained substantial [21]. Long-term single-center experience has also reported sustained stabilization of lung function with acceptable safety during prolonged sirolimus therapy [34].

The divergence between relatively stable spirometry and continuing decline in TLCO is frequently described in LAM and may reflect progressive cystic destruction and vascular/lymphatic involvement. Comprehensive monitoring beyond spirometry alone remains important, as recommended by guidelines [2]. In addition, recent modelling work in treatment-naïve cohorts suggests that individualized prediction of lung function trajectories may support risk-stratified monitoring and earlier therapeutic decisions in LAM [35].

Lymphatic manifestation is a major driver of morbidity. Complete resolution of chylous effusions and substantial regression of lymphangioleiomyomomas reinforce the marked sensitivity of lymphatic manifestations to mTOR inhibition, consistent with prior reports, including lower-dose strategies [22,36–38].

Pneumothorax remains a hallmark complication of LAM. A historical prospective self-controlled registry analysis reported lower recurrence during sirolimus exposure compared with untreated periods [39–41]. Similar signals have been described after surgical pleural covering strategies combined with sirolimus [42]. In our study, pneumothorax during sirolimus therapy was infrequent and occurred only in patients with a prior history of pneumothorax. Although the small number of events precludes causal inference, these findings are consistent with a potential protective effect of adequate mTOR inhibition.

Although we observed exploratory exposure–AE signals, trough levels were not associated with functional response or AEs in MILES [44]. Lower-dose strategies (target trough ≤5

ng/mL) have shown comparable benefit in some cohorts, particularly for lymphatic manifestations [36]. Therefore, the optimal trough range likely depends on treatment goals and patient factors within a structured monitoring framework [2,22,44].

Beyond mTOR inhibition, the therapeutic landscape in LAM continues to evolve, with growing interest in adjunctive and phenotype-directed strategies, particularly in patients with progressive structural lung disease despite standard treatment. Recent reviews summarize several emerging approaches, including antifibrotic concepts and combination strategies, although their precise role in routine clinical care remains to be defined [45,46].

Limitations include the retrospective single-center design, variable completeness across time points and the absence of a comparator; event counts were small for some outcomes. Strengths include detailed phenotyping, clinically relevant lymphatic and extrapulmonary outcomes with volumetric imaging, and extended follow-up reflecting routine practice.

Conclusions In a real-world cohort of patients with LAM treated at a national tertiary referral center, sirolimus was associated with long-term stabilization of lung function, regression of AML volume, and substantial improvement of lymphatic manifestations (including complete resolution of chylous effusions), with an acceptable safety profile. In exploratory analyses, functional deterioration and on-treatment pneumothorax were observed more often among patients with treatment interruptions and/or lower sirolimus trough concentrations; however, event counts were small and causality cannot be inferred. These findings support continued use of individualized sirolimus regimens with structured monitoring in patients with progressive or clinically significant LAM [2,12].

Supplementary material

Supplementary material is available at www.mp.pl/paim.

Article information

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Contribution statement JNE and KB conceived the study, organized the project, analyzed and interpreted the data, drafted the manuscript, and contributed equally to this work. KB performed the statistical analysis. ER had full access to the data, takes responsibility for the integrity of the data, and contributed substantially to the study design, organization, data analysis, interpretation, and manuscript review. AR and PS contributed substantially to the study design, performed the experiments, and analyzed the results. RL contributed substantially to the histopathological assessment, data collection, interpretation, and manuscript review and approval. IB and KB contributed substantially to the radiological assessments, data collection, interpretation, and manuscript review and approval. MS contributed substantially to patient recruitment, data interpretation, and manuscript review and approval. MAP, JChW, and JMD contributed substantially to study organization, data interpretation, and manuscript review and approval.

Conflict of interest None declared.

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Table 1. Baseline demographic, functional and laboratory characteristics of the studied lymphangioleiomyomatosis groups

Variable	**All patients (n=71)**	**sLAM (n=57)**	**TSC-LAM (n=14)**	**P-value**
Age at diagnosis, years; mean (SD)	38.9 (9.0)	40.4 (8.7)	33.0 (7.7)	0.005
Age at sirolimus initiation, years; median [IQR]	40.0 [33.0–48.0]	42.0 [35.0–48.0]	34.0 [30.5–38.0]	0.01
Female sex, n (%)	70 (99)	57/57 (100)	13/14 (93)	0.20
Diagnostic delay, months; median [IQR]	24.0 [6.5–54.0]	24.0 [6.0–60.0]	30.0 [12.2–36.0]	0.58
Ever-smoker, n (%)	24/71 (34)	22/57 (39)	2/14 (14)	0.12
Smoking, pack-years; mean (SD)	2.9 (6.1)	3.4 (6.5)	1.1 (3.3)	0.174
Pneumothorax, n (%)	27/71 (38)	25/57 (44)	2/14 (14)	0.06
Chylous effusion, n (%)	15/71 (21)	14/57 (25)	1/14 (7)	0.27
Lymphangioleiomyoma, n (%)	28/71 (39)	26/57 (46)	2/14 (14)	0.03

Variable	All patients (n=71)	sLAM (n=57)	TSC-LAM (n=14)	P-value
Renal angiomyolipoma, n (%)	33/71 (46)	22/57 (39)	11/14 (79)	0.007
PEComa, n (%)	18/71 (25)	16/57 (28)	2/14 (14)	0.49
Asthma, n (%)	29/71 (41)	27/57 (47)	2/14 (14)	0.02
Arterial hypertension, n (%)	28/71 (39)	23/57 (40)	5/14 (36)	>0.99
Overweight, n (%)	3/71 (4)	1/57 (2)	2/14 (14)	0.10
FEV1, L; median [IQR]	2.06 [1.54–2.65]	1.94 [1.30–2.41]	2.96 [2.66–3.13]	<0.001
FEV1, % predicted; mean (SD)	68.7 (20.5)	65.1 (19.0)	84.7 (20.1)	<0.001
FEV1 <70% predicted, n/N (%)	35/70 (50)	34/57 (60)	1/13 (8)	<0.001
FVC, L; mean (SD)	3.11 (0.68)	3.00 (0.63)	3.53 (0.78)	0.005
FVC, % predicted; mean (SD)	85.2 (18.1)	83.7 (18.7)	91.3 (15.0)	0.12
TLCO, mL/min/mmHg; median [IQR]	4.54 [3.01–6.30]	3.73 [2.79–5.66]	6.73 [5.87–7.15]	<0.001
TLCO, % predicted; median [IQR]	57 [35–72]	43 [33–65]	74.5 [69–79]	<0.001
6MWD, m; median [IQR]	510 [454–570]	510 [445–550]	500 [462–570]	0.71
Resting capillary pO2, mmHg; mean (SD)	76.7 (12.2)	77.2 (12.3)	74.9 (12.0)	0.53
VEGF-D, pg/mL; median [IQR]	1648 [874–2992]	1644 [870–3000]	1690 [954–2517]	0.76

Legend: Values are presented as mean (SD), median [IQR], or n (%), as appropriate.

Normality of continuous variables was assessed using the Shapiro-Wilk test. Between-group

comparisons used Student's t test or Mann-Whitney U test for continuous variables and χ^2 test or Fisher's exact test for categorical variables, as appropriate.

Abbreviations: 6MWD, 6-minute walk distance; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; IQR, interquartile range; LAM, lymphangioleiomyomatosis; PEComa, perivascular epithelioid cell tumor; SD, standard deviation; sLAM, sporadic LAM; TLCO, transfer factor of the lung for carbon monoxide; TSC-LAM, tuberous sclerosis complex-associated LAM; VEGF-D, vascular endothelial growth factor D.

Table 2. Change from baseline in pulmonary function and exercise capacity during sirolimus treatment in the overall cohort

Parameter	Baseline	n pairs 3 m	Δ 3 months	P-value	n pairs 1 y	Δ 1 year	P-value	n pairs 2 y	Δ 2 years	P-value	n pairs 5 y	Δ 5 years	P-value
FVC, L	3.11 (0.68)	65	0.11 [0.00–0.30]	<0.001	67	0.11 [−0.07 to 0.37]	<0.001	51	0.11 [−0.11 to 0.31]	0.04	42	0.02 [−0.36 to 0.29]	0.75
FVC, % predicted	85.2 (18.1)	63	3.0 [0.0–9.0]	<0.001	66	3.5 [−1.0 to 12.0]	<0.001	51	4.0 [−1.5 to 10.0]	0.005	41	3.0 [−6.0 to 12.0]	0.12

Parameter	Baseline	n pairs 3 m	Δ 3 months	P-value	n pairs 1 y	Δ 1 year	P-value	n pairs 2 y	Δ 2 years	P-value	n pairs 5 y	Δ 5 years	P-value
FEV1, L	2.06 [1.54–2.65]	62	0.10 [0.00–0.31]	<0.001	66	0.03 [−0.10 to 0.30]	0.03	51	0.03 [−0.11 to 0.26]	0.19	42	−0.05 [−0.20 to 0.20]	0.57
FEV1, % predicted	69.3 (20.5)	62	4.0 [0.0–10.0]	<0.001	65	4.0 [−3.0 to 11.0]	0.001	50	2.0 [−3.0 to 10.0]	0.03	41	2.0 [−7.0 to 10.0]	0.34
TLC, L	5.53 (1.01)	50	0.13 [−0.16 to 0.35]	0.02	56	0.06 [−0.15 to 0.35]	0.08	46	0.02 [−0.14 to 0.28]	0.22	39	−0.13 [−0.42 to 0.30]	0.31
TLC, % predicted	110.3 (21.1)	50	2.3 [−2.8 to 8.0]	0.03	56	2.0 [−3.0 to 8.2]	0.11	46	0.5 [−3.0 to 4.8]	0.35	39	−3.0 [−9.5 to 7.0]	0.36

Parameter	Baseline	n pairs 3 m	Δ 3 months	P-value	n pairs 1 y	Δ 1 year	P-value	n pairs 2 y	Δ 2 years	P-value	n pairs 5 y	Δ 5 years	P-value
RV, L	2.29 [1.83–2.81]	50	−0.02 [−0.18 to 0.13]	0.55	56	−0.10 [−0.21 to 0.12]	0.10	46	−0.03 (0.32)	0.58	39	−0.07 (0.47)	0.39
RV, % predicted	142 [114–167]	50	−2.0 [−10.8 to 10.0]	0.56	56	−6.1 [−15.5 to 4.5]	0.04	46	−4.5 (20.6)	0.15	39	−10.1 (28.1)	0.03
TLCO, mL/min/mmHg	4.54 [3.01–6.30]	57	0.15 [−0.17 to 0.52]	0.053	60	0.16 [−0.26 to 0.61]	0.08	46	0.01 [−0.40 to 0.49]	0.56	40	−0.19 [−0.49 to 0.24]	0.31
TLCO, % predicted	57 [35–72]	57	2.0 [−2.0 to 6.0]	0.07	60	1.5 [−3.0 to 8.0]	0.04	46	1.0 [−4.0 to 6.8]	0.26	40	−1.0 [−5.5 to 5.0]	0.95

Parameter	Baseline	n pairs 3 m	Δ 3 months	P-value	n pairs 1 y	Δ 1 year	P-value	n pairs 2 y	Δ 2 years	P-value	n pairs 5 y	Δ 5 years	P-value
6MWD, m	510 [454–570]	65	30 [0–50]	<0.001	63	30 [0–76]	<0.001	50	30 [0–68]	<0.001	38	35 [−15 to 70]	0.07
Oxygen desaturation during 6MWT, %	3 [1–9]	64	0 [−1 to 1]	0.31	63	0 [−1 to 1]	0.30	50	0 [−2 to 2]	0.84	38	1.0 (4.4)	0.16
PaO2, mmHg	76.7 (12.2)	59	1.4 [−1.7 to 5.3]	0.02	58	0.7 (8.0)	0.49	42	−1.0 [−6.1 to 4.0]	0.77	38	−0.4 (8.2)	0.77

Legend: Values are presented as mean (SD) when approximately normally distributed and as median [IQR] otherwise. Follow-up columns show change from baseline among patients with paired baseline and follow-up measurements. The number of paired observations is shown separately for each comparison. P-values are for paired comparisons versus baseline.

Abbreviations: 6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PaO2, arterial partial pressure of oxygen; RV, residual volume; TLC, total lung capacity; TLCO, transfer factor of the lung for carbon monoxide.

Table 3. Change from baseline in pulmonary function and exercise capacity during sirolimus treatment in patients with baseline chylous effusion (n=15)

Parameter	Baseline	n pairs 3 m	Δ 3 months	P-value	n pairs 1 y	Δ 1 year	P-value	n pairs 2 y	Δ 2 years	P-value	n pairs 5 y	Δ 5 years	P-value
FVC, L	2.69 (0.58)	15	0.17 [−0.01 to 0.40]	0.04	14	0.14 [−0.08 to 0.65]	0.07	11	0.19 [0.12 – 0.46]	0.03	10	0.37 (0.86)	0.21
FVC, % predicted	74.5 (16.2)	15	4.0 [−1.0 to 11.0]	0.050	13	6.0 [−1.0 to 17.0]	0.03	11	6.0 [4.0–12.5]	0.004	10	11.8 (22.4)	0.13
FEV1, L	1.94 (0.53)	15	0.15 [0.06–0.50]	0.002	13	0.33 (0.68)	0.11	11	0.30 [0.06 – 0.64]	0.007	10	0.38 (0.71)	0.12
FEV1, % predicted	65.5 (15.7)	15	5.0 [3.0–12.5]	0.001	13	5.0 [3.0–25.0]	0.009	11	10.0 [5.5–19.0]	0.002	10	14.2 (22.4)	0.08
TLC, L	5.83 (1.23)	9	0.20 (0.59)	0.34	11	0.00 [−0.1	0.85	10	−0.06	0.50	8	−0.32	0.23

Parameter	Baseline	n pairs 3 m	Δ 3 months	P-value	n pairs 1 y	Δ 1 year	P-value	n pairs 2 y	Δ 2 years	P-value	n pairs 5 y	Δ 5 years	P-value
						3 to 0.28]			(0.29)			(0.69)	
TLC, % predicted	119.6 (27.6)	9	4.1 (12.5)	0.35	11	−1.5 (20.3)	0.81	10	−1.5 [−7.7 to 1.0]	0.24	8	−11.3 (22.6)	0.20
RV, L	2.58 (0.61)	9	−0.01 (0.31)	0.92	11	−0.01 (0.38)	0.94	10	−0.06 (0.43)	0.67	8	0.18 (0.62)	0.43
RV, % predicted	154.0 (29.9)	9	−0.6 (18.5)	0.92	11	−1.8 (22.5)	0.79	10	−6.9 (25.2)	0.41	8	3.1 (34.2)	0.81
TLCO, mL/min/mm Hg	3.93 (1.41)	12	0.27 [−0.06 to 1.17]	0.08	11	0.65 (1.21)	0.11	9	0.75 (1.21)	0.10	8	0.59 (1.35)	0.26
TLCO, % predicted	46.6 (16.1)	12	2.5 [−0.8	0.11	11	7.5 (13.7)	0.10	9	8.7 (14.0)	0.10	8	7.5 (15.5)	0.21

Parameter	Baseline	n pairs 3 m	Δ 3 months	P-value	n pairs 1 y	Δ 1 year	P-value	n pairs 2 y	Δ 2 years	P-value	n pairs 5 y	Δ 5 years	P-value
			to 13.8]										
6MWD, m	473 (105)	14	33 (35)	0.004	13	51 (56)	0.007	11	72 (56)	0.002	9	45 (82)	0.14
Oxygen desaturation during 6MWT, %	3.0 [1.5–9.5]	14	0.0 [−0.8 to 0.8]	0.89	13	0.0 [−2.0 to 1.0]	0.97	11	2.0 [−1.0 to 2.5]	0.26	7	1.1 (3.9)	0.47
PaO2, mmHg	75.8 (10.9)	12	2.3 (6.9)	0.27	12	2.1 (9.0)	0.43	10	1.4 (7.4)	0.56	7	0.4 (9.3)	0.90

Legend: Values are presented as mean (SD) when approximately normally distributed and as median [IQR] otherwise. Follow-up columns show change from baseline among patients with paired baseline and follow-up measurements. The number of paired observations is shown separately for each comparison. P-values are for paired comparisons versus baseline.

Abbreviations: 6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PaO2, arterial partial pressure of oxygen; RV, residual volume; TLC, total lung capacity; TLCO, transfer factor of the lung for carbon monoxide.

Table 4. Spearman correlation coefficients between baseline serum VEGF-D and selected disease manifestations

Clinical manifestation	Spearman R	P
Chylous effusion	0.45	<0.001
Pneumothorax	-0.20	0.09
Angiomyolipoma	-0.08	0.53
Lymphangioleiomyoma	0.42	<0.001

Legend: Spearman rank correlation between baseline serum VEGF-D concentration and selected disease manifestations. R denotes Spearman's rank correlation coefficient; P denotes the two-sided P-value.

Abbreviations: VEGF-D, vascular endothelial growth factor D.

Table 5. Change from baseline in angiomyolipoma and lymphangioleiomyoma volume during sirolimus treatment

Lesion	**Time point**	**n pairs**	**Baseline volume, cm³**	**Follow-up volume, cm³**	**Δ volume, cm³**	**% change from baseline**	**P-value**
Lymphangioleiomyoma	3 months	25	157 [102–268]	65 [42–105]	−52 [−115 to −19]	−33 [−79 to −16]	<0.001
Lymphangioleiomyoma	1 year	25	149 [102–218]	48 [0–98]	−67 [−159 to −38]	−70 [−100 to −31]	<0.001

Lesion	Time point	n pairs	Baseline volume, cm³	Follow-up volume, cm³	Δ volume, cm³	% change from baseline	P-value
Lymphangioleiomyoma	2 years	21	159 [117–290]	42 [0–117]	−100 [−178 to −40]	−75 [−100 to −41]	<0.001
Lymphangioleiomyoma	5 years	15	167 [141–375]	0 [0–98]	−113 [−223 to −49]	−100 [−100 to −33]	<0.001
Angiomyolipoma	3 months	23	98 [44–142]	77 [31–126]	−13 [−27 to 0]	−14 [−19 to 0]	0.001
Angiomyolipoma	1 year	28	88 [32–168]	63 [28–140]	−7 [−37 to 0]	−13 [−30 to 0]	0.002
Angiomyolipoma	2 years	25	90 [56–172]	71 [38–138]	−19 [−48 to 0]	−19 [−45 to 0]	<0.001
Angiomyolipoma	5 years	14	69 [28–87]	60 [18–68]	−7 [−18 to −1]	−17 [−30 to −1]	0.005

Legend: Values are presented as median [IQR]. Analyses included only patients with measurable baseline lesions and paired baseline and follow-up MRI measurements. P-values are for paired comparisons versus baseline.

Abbreviations: AML, angiomyolipoma.

Short title: Sirolimus in LAM: long-term real-world outcomes