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Changes in Lung Function and Chylous Effusions in Patients With Lymphangioleiomyomatosis Treated With Sirolimus

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Abstract

Background—Lymphangioleiomyomatosis (LAM) is a disorder that affects women and is characterized by cystic lung destruction, chylous effusions, lymphangioleiomyomas, and angiomyolipomas. It is caused by proliferation of abnormal smooth muscle–like cells. Sirolimus is a mammalian target of rapamycin inhibitor that has been reported to decrease the size of neoplastic growths in animal models of tuberous sclerosis complex and to reduce the size of angiomyolipomas and stabilize lung function in humans.

Objective—To assess whether sirolimus therapy is associated with improvement in lung function and a decrease in the size of chylous effusions and lymphangioleiomyomas in patients with LAM.

Design—Observational study.

Setting—The National Institutes of Health Clinical Center.

Patients—19 patients with rapidly progressing LAM or chylous effusions.

Intervention—Treatment with sirolimus.

Measurements—Lung function and the size of chylous effusions and lymphangioleiomyomas before and during sirolimus therapy.

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Results—Over a mean of 2.5 years before beginning sirolimus therapy, the mean (±SE) FEV_1 decreased by 2.8% ± 0.8% predicted and diffusing capacity of the lung for carbon monoxide (D_{LCO}) decreased by 4.8% ± 0.9% predicted per year. In contrast, over a mean of 2.6 years of sirolimus therapy, the mean (± SE) FEV_1 increased by 1.8% ± 0.5% predicted and D_{LCO} increased by 0.8% ± 0.5% predicted per year ($P < 0.001$). After beginning sirolimus therapy, 12 patients with chylous effusions and 11 patients with lymphangioleiomyomas experienced almost complete resolution of these conditions. In 2 of the 12 patients, sirolimus therapy enabled discontinuation of pleural fluid drainage.

Limitations—This was an observational study. The resolution of effusions may have affected improvements in lung function.

Conclusion—Sirolimus therapy is associated with improvement or stabilization of lung function and reduction in the size of chylous effusions and lymphangioleiomyomas in patients with LAM.

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Lymphangioleiomyomatosis (LAM) is a multisystem disorder that affects primarily women and is characterized by proliferation of abnormal smooth muscle–like cells (LAM cells) that lead to cystic lung destruction, lymphatic masses (for example, lymphangioleiomyomas), and abdominal angiomyolipomas (1, 2). Lymphangioleiomyomatosis that occurs in patients with no evidence of genetic disease is known as *sporadic LAM*. Lymphangioleiomyomatosis also occurs in approximately one third of women with tuberous sclerosis complex (TSC) (3–5), an autosomal dominant syndrome that is caused by mutations in the *TSC1* or *TSC2* gene and is characterized by hamartomatous growths in various organs (6, 7). Mutations in the *TSC2* gene and loss of heterozygosity of *TSC2* have been reported in LAM-related lung lesions from patients with sporadic LAM, which suggests that mutations in the *TSC* genes may cause sporadic LAM as well as LAM associated with TSC (8, 9).

Persons with LAM may present with dyspnea, pneumothorax, thoracoabdominal lymphangioleiomyomas (1, 2, 10, 11), chylous effusions (12–17), or abdominal hemorrhage caused by angiomyolipomas (18, 19). Lymphangioleiomyomas occur in approximately 21% of persons with LAM and may cause abdominal pain, obstipation, the Horner syndrome, a malabsorption syndrome, and bladder obstruction (10, 14–17). The clinical course of LAM is highly variable (20). This condition was originally described as a fatal disease affecting women of child-bearing age, but LAM also occurs in postmenopausal women and can be a chronic disease associated with a life expectancy spanning decades (21). Although younger, premenopausal patients seem to have more aggressive lung disease (20), accurate predictors of disease course or severity are unknown.

Recommended therapies for LAM have included oophorectomy and antiestrogenic agents, such as progesterone and gonadotropin-releasing hormone analogues, but no evidence has shown that these treatments are effective (20). Effective treatments also are lacking for patients with rapidly progressing lung disease or morbid symptoms caused by chylous effusions or lymphangioleiomyomas associated with LAM.

Lymphangioleiomyomatosis is caused by a deficiency of hamartin and tuberin, 2 proteins encoded by *TSC1* and *TSC2* genes, respectively. These proteins regulate the mammalian target of rapamycin (mTOR) through a guanine nucleotide–binding protein called *Ras homolog enriched in brain* (*Rheb*) (22–27). Deficiency of hamartin or tuberin due to mutations of the *TSC1* or *TSC2* gene leads to increased activation of Rheb, upregulation of mTOR, and abnormal cellular growth (22–26).

The immunosuppressant sirolimus inhibits mTOR and has been shown to decrease the size of neoplastic growths in animal models of TSC (28–30). Sirolimus therapy was reported to be associated with decreased size of angiomyolipomas and improved or stabilized lung function in humans with LAM or TSC (31, 32). Case reports also describe resolution of chylous effusions and lymphangioleiomyomas after sirolimus therapy (33–35). In addition, therapy with everolimus, another mTOR inhibitor, was associated with reductions in the size of giant cell astrocytomas and in the frequency of seizures in patients with TSC (36).

The MILES (Multicenter International LAM Efficacy of Sirolimus) Trial, a recently completed double-blind, placebo-controlled trial, showed that sirolimus stabilized lung function and was associated with a reduction in symptoms and improvement in quality of life in patients with LAM (37). However, patients with pleural effusions were excluded from this study because of the potential effects on pulmonary function. TESSTAL (Trial of Efficacy and Safety in Sirolimus) is an ongoing study in the United Kingdom that is focused on changes in angiomyolipomas. However, because the planned enrollment for this trial is only 14 participants and includes participants of both sexes, the trial is unlikely to definitively evaluate lung function or to include a substantial number of patients with pleural effusions and lymphatic involvement.

We sought to evaluate the effect of sirolimus in patients with LAM who had rapidly progressive or severe lung disease and in those with chylous effusions and lymphangioleiomyomas, a population in whom sirolimus has not been tested. Because these patients were participating in a natural history study at the National Institutes of Health (NIH), we had their physiologic and radiologic data for several years before initiation of sirolimus therapy and were able to compare data obtained before and after therapy.

Methods

Patients

Our study included 19 patients with LAM who were participating in a natural history protocol at the NIH Clinical Center (National Heart, Lung, and Blood Institute [NHLBI] protocol 95-H-0186) and had received off-label sirolimus therapy. The natural history protocol had been designed to define the clinical course of LAM, elucidate the pathogenesis of the disease at the cellular and molecular levels, and develop more effective therapy for this condition. Participants underwent a tissue biopsy that was diagnostic of LAM in 13 patients, whereas 6 patients had a history of dyspnea or pneumothorax with evidence of cystic lung lesions on axial computed tomography (CT) of the chest plus extrapulmonary disease, such as angiomyolipoma, chylous effusion, or lymphangioleiomyomas. All 19 patients participating in the drug trial had either progressive disease or chylous effusions.

We included all patients who received sirolimus therapy in our analysis. Patients decided to receive off-label sirolimus therapy after consultation with their local physicians. Five patients began off-label sirolimus therapy before enrollment in the MILES Trial was available, 11 patients had pleural effusions that excluded them from this trial, and 3 patients chose not to participate.

Local physicians prescribed sirolimus therapy to patients in our trial and monitored serum sirolimus levels and potential toxicity. Every 3 to 12 months, patients underwent blood work, measurement of serum sirolimus levels, pulmonary function tests, and chest radiography. Computed tomography of the thorax and abdomen were performed once a year or when medically indicated. This study was approved by the institutional review board of the NHLBI, NIH.

Chest Radiography and CT

A General Electric HiSpeed Advantage Unit (GE Medical Systems, Milwaukee, Wisconsin) was used to perform CT of the lungs with 8.0- to 10.0-mm collimation at 1.0-cm intervals. In addition, all patients underwent CT with 1.0-mm collimation (high-resolution CT) at 3.0-cm intervals. Computed tomography of the abdomen was performed as reported elsewhere (11).

Pulmonary Function Tests

Lung volumes, flow rates, and single-breath D_{LCO} were measured (SensorMedics Vmax 229, Yorba Linda, California) according to the standards of the American Thoracic Society and European Respiratory Society (38, 39).

Study End Points

End points were changes in lung function, chylous effusions, and lymphangioleiomyomas.

Statistical Analysis

We evaluated changes in lung function associated with sirolimus therapy by using mixed-effects models. A time-dependent group indicator and adjustment for baseline results of pulmonary function tests were used in all models. The nonparametric sign test was used to evaluate changes in the size of lymphangioleiomyomas associated with sirolimus therapy. All reported *P* values are 2-sided, and data are reported as means (±SEs). Age data are reported as means (SDs).

Role of the Funding Source

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Results

Study Population

Mean patient age at the time of enrollment in the NHLBI natural history protocol was 36.9 years (SD, 9.8). Mean age at presentation of LAM-related symptoms was 34.6 years (SD, 9.4); a definite diagnosis was established at age 36.6 years (SD, 8.7). Treatment with sirolimus was started at age 41.0 years (SD, 9.0). The mean interval between diagnosis to initiation of sirolimus therapy was 4.4 years (SD, 3.7), and the average patient age at the last physician visit during the study was 43.6 years (SD, 8.8).

At enrollment, 13 patients received oxygen therapy. Twelve patients had chylous effusions, and 11 patients had lymphangioleiomyomas. Five patients had renal angiomyolipomas. Initial presentation before diagnosis of LAM was pneumothorax in 9 patients, dyspnea in 5 patients, and abdominal masses in 5 patients. No patient had TSC.

Five patients had previous pregnancies, 3 patients were menopausal, 5 patients had received progesterone therapy, and 2 patients had received leuprolide therapy. No patient had previously undergone oophorectomy. Five patients were former smokers, and the rest were nonsmokers. All patients had progressive signs or symptoms that were attributable to LAM.

Changes in Study Outcomes With Sirolimus Therapy

Lung Function—Figure 1 shows the percent predicted FEV_1 and D_{LCO} at each NIH visit before and after beginning sirolimus therapy in 18 patients (1 patient could not undergo

these tests because of chest tube drainage). Results of the adjusted analysis obtained by using mixed-effects models showed statistically significant differences in the annual rate of change in FVC, FEV_1, and D_{LCO} before and after sirolimus therapy.

Over a mean duration of 2.5 ± 1.2 years before initiation of sirolimus therapy, FVC decreased by 50 ± 30 mL per year (1.2% ± 0.6% predicted), FEV_1 decreased by 100 ± 30 mL per year (2.8% ± 0.8% predicted), and D_{LCO} decreased by 1.1 ± 0.1 mL/min per mm Hg (4.8% ± 0.9% predicted) per year (Figure 2). In contrast, over a mean of 2.6 ± 1.2 years of sirolimus therapy, FVC increased by 90 ± 20 mL per year (3.2% ± 0.5% predicted; $P < 0.001$), FEV_1 increased by 50 ± 20 mL per year (1.8% ± 0.5% predicted; $P < 0.001$), and D_{LCO} increased by 0.2 ± 0.1 mL/min per mm Hg (0.8% ± 0.5% predicted; $P < 0.001$) per year (Figure 2). Statistically significant increases in FVC (80% ± 5% predicted to 88% ± 5% predicted; $P < 0.001$), FEV_1 (62% ± 7% predicted to 69% ± 7% predicted; $P < 0.010$), and D_{LCO} (40% ± 4% predicted to 45% ± 5% predicted; $P < 0.026$) were observed within 6 months (0.4 ± 0.1 y) after initiation of sirolimus therapy in 14 of 18 patients for whom early lung function data were available.

To determine whether lung function improvement was independent of the resolution of chylous effusions, data from 7 patients without effusions were analyzed further. In this subgroup, FEV_1 decreased by 110 ± 10 mL per year before initiation of sirolimus therapy compared with a decrease of 10 ± 10 mL per year after beginning sirolimus therapy ($P = 0.002$). The D_{LCO} decreased by 0.5 ± 0.2 mL/min per mm Hg per year before initiation of sirolimus therapy compared with an increase of 0.04 ± 0.1 mL/min per mm Hg per year after sirolimus therapy was started ($P = 0.020$). Forced vital capacity increased by 50 ± 40 mL per year before initiation of sirolimus therapy compared with an increase of 110 ± 30 mL per year after sirolimus therapy was started ($P = 0.162$).

The Appendix Table (available at www.annals.org) shows complete pulmonary function data obtained at study enrollment for 18 patients immediately before initiation of sirolimus therapy and at the most recent follow-up visit.

Chylous Effusions—Twelve patients had chylous effusions. Eleven patients had pleural effusions, 7 of whom also had ascites (Table). One patient had only ascites. Of the 11 patients with pleural effusions, 8 patients had them at the time of enrollment in the natural history protocol. In the remaining 3 patients, chylous effusions were noted 3 to 12 months after enrollment. Chylous effusions had been present for a minimum of 1.5 ± 0.4 years before initiation of sirolimus therapy. Before sirolimus therapy, all patients had undergone thoracentesis, and 2 patients had required chest tube drainage. Pleurodesis had been performed in 12 of the 19 patients, but this intervention prevented recurrence of pleural effusions in only 1 patient.

Before sirolimus therapy, the sizes of the effusions had not substantially decreased except on drainage by thoracentesis or the placement of a chest tube. During sirolimus therapy, 9 patients had complete resolution of the pleural effusions (Figure 3, *A* and *B*). Four of these effusions were large, 3 were moderate in size, and 2 were small.

Complete resolution of effusions was noted after 410 ± 111 days of therapy; in 6 patients, effusions resolved after 131 ± 61 days of therapy. Of the 2 patients with partially resolved effusions, 1 patient had large effusions that required frequent drainage before beginning sirolimus therapy and the other patient had a small effusion. The average duration of sirolimus therapy for all patients with effusions was 2.4 ± 1.0 years. All 8 patients with ascites had complete resolution.

Two patients had dramatic responses to sirolimus therapy. A 29-year-old woman with recurrent chylous pleural effusions despite chest tube drainage and talc pleurodesis had required thoracentesis as frequently as once every week for 7 months; this intervention was associated with a total weight loss of 11 kg. After 6 months of sirolimus therapy, further thoracentesis was not required (Figure 3, *A* and *B*). After 30 months of therapy, the effusions resolved completely, and the patient's body mass index increased from 21 to 25 kg/m^2.

A 62 year-old woman in whom chemical pleurodesis was unsuccessful had persistent pleural fluid drainage averaging 1500 to 3000 mL/d despite a low-fat diet and administration of octreotide. After 4 weeks of sirolimus therapy, a substantial decrease in drainage volume to less than <200 mL/d and in the size of the lymphangioleiomyomas was noted and the chest tube was removed. Six months after initiation of sirolimus therapy, the pleural effusion had resolved almost completely (Appendix Figure, available at www.annals.org).

Lymphangioleiomyomas—Eleven patients had lymphangioleiomyomas averaging 114 ± 50 mL in volume (Table). During sirolimus therapy, the tumors resolved completely in 9 patients. In the remaining 2 patients, the volume of the tumors decreased from 44 ± 22 mL to 17 ± 13 mL ($P < 0.001$, nonparametric sign test) (Table and Figure 3, *E* and *F*). Lymphangioleiomyomas and chylous effusions tended to resolve concurrently.

Angiomyolipomas—Of the 5 patients with angiomyolipomas, 2 had a substantial decrease in tumor size during sirolimus therapy. The tumor decreased from 12 to 8 mL in 1 patient and from 12 to 4 mL in another patient. In a third patient, tumor size could not be assessed because the tumor was intermixed with the kidney parenchyma. A fourth patient had angiomyolipomas that were too small for measurement, and the fifth patient did not undergo follow-up abdominal CT.

Dose of Sirolimus

The mean dosage of sirolimus was 2.6 ± 0.9 mg/d (range, 1 to 5 mg/d), and the average duration of therapy was 2.6 ± 1.2 years (range, 0.7 to 5.4 y). The sirolimus dose was adjusted by the patient's local physician to achieve serum levels between 5 and 15 ng/mL. The Table shows the mean serum sirolimus level for each patient. The mean total dose of sirolimus was 2447 ± 1663 mg (range, 532 to 6425 mg).

Adverse Events Potentially Related to Sirolimus

Adverse events that were probably related to sirolimus therapy included mouth ulcers in 8 patients, hyperlipidemia in 8 patients, acne in 6 patients, 3 cases of worsening hypertension, 3 cases of diarrhea, and 1 case of persistent mild neutropenia (Table). The mean leukocyte count and total neutrophil count at the patients' last physician visit were 5.4 ± 0.3 × 10^9 cells/L (range, 2.8 to 4.8 × 10^9 cells/L) and 3.4 ± 0.3 × 10^9 cells/L (range, 1.4 to 5.8 × 10^9 cells/L), respectively. Mean total and low-density lipoprotein cholesterol levels were, respectively, 4.95 ± 0.23 mmol/L (range, 3.85 to 7.30 mmol/L) (191 ± 9 mg/dL [range, 149 to 282 mg/dL]) and 3.11 ± 0.21 mmol/L (range, 1.94 to 5.08 mmol/L) (120 ± 8 mg/dL [range, 75 to 196 mg/dL]). Six of the 8 patients with hyperlipidemia received statin therapy.

One patient had a major skin infection secondary to pneumococcal vaccination that required temporary discontinuation of sirolimus therapy and administration of antibiotics. No other patient had to discontinue sirolimus therapy because of adverse events. Local physicians managed all adverse events.

Discussion

We found that treatment with sirolimus was associated with improvement or stabilization of lung function and decrease in the size of chylous effusions and lymphangioleiomyomas in a selected population of patients with LAM. Of note, adverse events associated with sirolimus therapy were manageable and, as of now, all patients continue to receive this therapy and have sustained improvement or stabilization of lung function and continued resolution of effusions and lymphangioleiomyomas.

Although previous reports have described improvement (31) or stabilization (32, 37) of lung function associated with sirolimus therapy, we believe that our study is the first to systematically evaluate the effect of sirolimus in patients with chylous effusions and lymphangioleiomyomas. In this subgroup of patients, sirolimus therapy was associated with reduction or resolution of the effusions and lymphangioleiomyomas, with consequent dramatic improvement in lung function. Patients with uncontrolled pleural effusions that required frequent pleural drainage no longer required repeated drainage after beginning sirolimus therapy. Another strength of our study is the body of both radiologic and physiologic information spanning several years preceding treatment with sirolimus, which provides a valuable basis for comparison with posttherapy data.

In patients without baseline pleural effusions, lung function during sirolimus therapy stabilized and, in contrast to the characteristic progressive nature of LAM (20, 40–42), no substantial decline in lung function was observed. This finding suggests that the beneficial effects of sirolimus therapy in patients with LAM may extend to those without involvement of the lymphatic system, although our small sample limits robust conclusions. Overall, however, our data are consistent with those of the recently completed MILES Trial (37), which showed that 1 year of sirolimus therapy was associated with stabilized lung function and reported changes in FEV_1 in the placebo and sirolimus groups that were similar to those in our study (Figure 2).

Our hypothesis was that suppression of LAM cell proliferation and growth by the sirolimus-mediated inhibition of the mTOR pathway would improve lung function and reduce the size of chylous effusions and lymphangioleiomyomas. This hypothesis was based on previous studies showing that sirolimus reduced the size of neoplastic growths in animal models of TSC (28–30). A literature search of the PubMed database for all articles related to sirolimus therapy in human patients with LAM through 2010 revealed individual case reports of reduction in the size of chylous effusions and lymphangioleiomyomas (33–35) and improved lung function in a series of patients treated for 1 year (31). Reductions in the size of angiomyolipomas (31) and giant cell astrocytomas in patients with LAM or TSC have also been reported (36). Now, the MILES Trial (37) and our data show that sirolimus therapy is associated with stabilization of lung function. Our study, however, extends these observations to patients with LAM and lymphatic involvement.

During the observation year of the MILES Trial, when patients did not receive sirolimus therapy, changes in FEV_1 and FVC in the sirolimus and placebo groups did not significantly differ, which indicates that the beneficial effects of sirolimus ceased after sirolimus therapy was discontinued (37). Our study shows that the benefits of sirolimus seem to be sustained for more than 2 years of therapy as long as patients continue to receive the drug. In addition, as in the MILES Trial, the adverse events associated with sirolimus in our study were manageable.

The MILES Trial (37) also showed that levels of serum vascular endothelial growth factor-D (VEGF-D), a lymphangiogenic growth factor implicated in the pathophysiology of LAM, were reduced in response to sirolimus, and that a decrease in mean VEGF-D levels even

after discontinuation of the drug was consistent with a sustained effect on the lymphatic component of the disease. Because VEGF-D levels are reported to be higher in patients with LAM and lymphatic involvement than in those with cystic disease limited to the lung (14), the data from the MILES Trial (37) are consistent with our finding that lymphatic involvement in LAM seems to be highly responsive to sirolimus therapy.

Our study has limitations. The selected LAM population in our study consisted of patients with progressive disease, most of whom had lymphatic involvement and chylous effusions. The rates of decline in pulmonary function observed in our patients before sirolimus therapy were higher than those previously reported (20, 40–42). In other studies, reported rates of decline in FEV_1 have ranged from 75 ± 9 mL per year to 118 ± 21 mL per year (20, 40, 41) and rates of decline in D_{LCO} have ranged from 0.69 ± 0.07 mL/min per mm Hg to 0.90 ± 0.26 mL/min per mm Hg per year (20, 40); each of these values is less than one half of the unadjusted rates of decline in pulmonary function that our patients experienced.

In a large previous study, the rates of decline in percentage of predicted FEV_1 and D_{LCO} were 1.7% ± 0.4% predicted and 2.4% ± 0.4% predicted per year, respectively (20). In our study, the average unadjusted rates of decline in FEV_1 and D_{LCO} were approximately 9% predicted per year, which reflects rapidly progressing severe disease.

A large difference in the rates of decline in FEV_1 between patients who present with dyspnea and those who present with pneumothorax has been reported (41). This finding suggests that LAM can be a very aggressive disease in some patients and can cause declines in FEV_1 or D_{LCO} ranging from 5% to 10% predicted per year, whereas in other patients, lung disease progresses slowly and interferes little with activities of daily living. Therefore, our findings cannot be generalized to patients with LAM who have milder disease without chylous effusions or lymphangioleiomyomas.

In addition, our study was not controlled, and it is possible that the pleural effusions may have resolved spontaneously. However, we have never observed spontaneous resolution of large chylous effusions in the NHLBI natural history protocol cohort.

Overall, our data suggest that sirolimus should be evaluated as a treatment of chylous effusions and symptomatic lymphangioleiomyomas in patients with LAM. As our study demonstrates, chylous effusions in LAM are difficult to treat and repeated thoracentesis may lead to severe weight loss. Other therapies, such as pleuroperitoneal shunts and octreotide, have been tried, but there is little experience with these therapeutic methods in patients with LAM (43–45). Although lymphangioleiomyomas are usually asymptomatic, compression of the bladder, bowel, pelvic veins, nerves, and other organs may cause pain, obstipation, frequent urination, and peripheral edema. Surgery has been performed but can lead to persistent lymphatic leakage, chylothorax, and ascites.

In conclusion, we found that sirolimus therapy was associated with improved or stabilized lung function and reductions in the size of chylous effusions and lymphangioleiomyomas in patients with aggressive LAM. Our findings suggest a potential role for sirolimus in the management of patients with LAM, especially for those with lymphatic involvement. The adverse events associated with sirolimus therapy were manageable in our patients. However, the long-term risks of sirolimus therapy must be weighed against its benefits, as we lack information regarding the optimal duration of therapy and when cessation should be considered. Lifelong therapy may be required, or resistance to sirolimus may eventually develop. Despite these possibilities, sirolimus therapy may be a reasonable consideration for patients with intractable chylous effusions and lymphangioleiomyomas.

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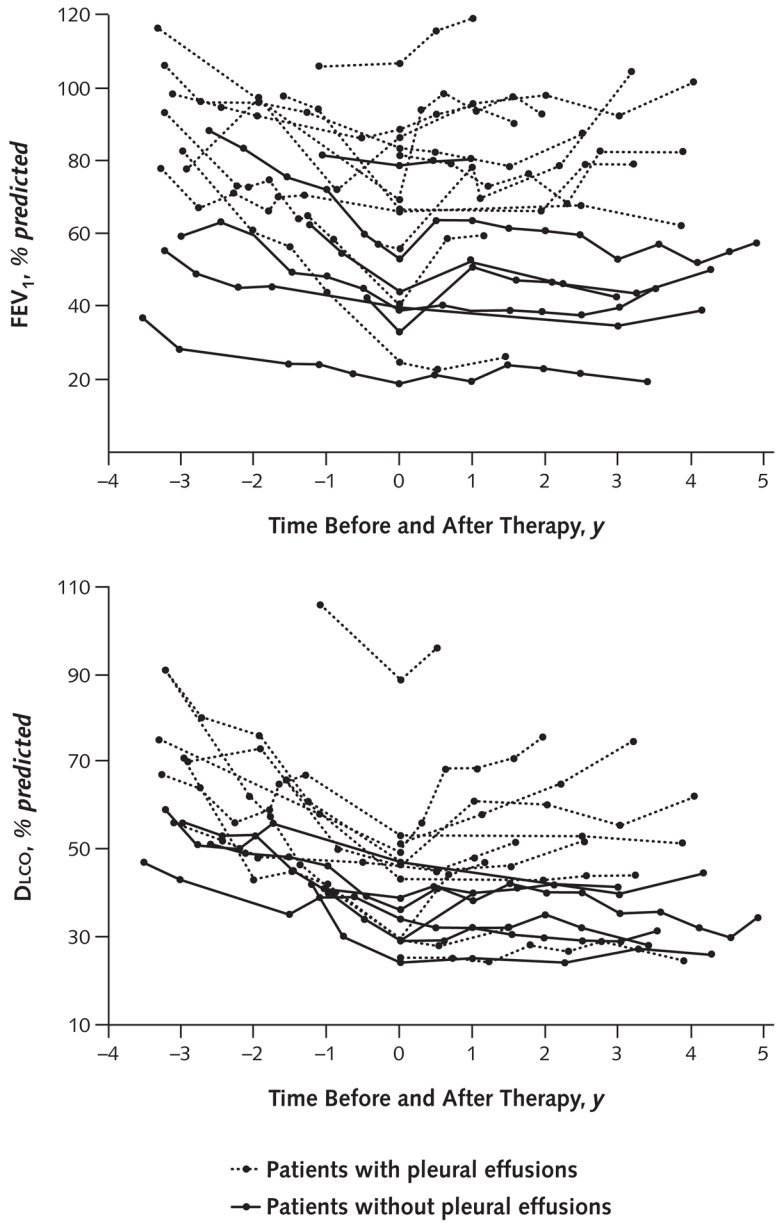


Figure 1. FEV_1 (*top*) and D_{LCO} (*bottom*) measurements obtained at each visit before and after sirolimus therapy

Data at 0 y were obtained just before starting sirolimus therapy. One of the 19 patients with chylothorax and continuous pleural drainage could not undergo pulmonary function tests. D_{LCO} = diffusing capacity of the lung for carbon monoxide.

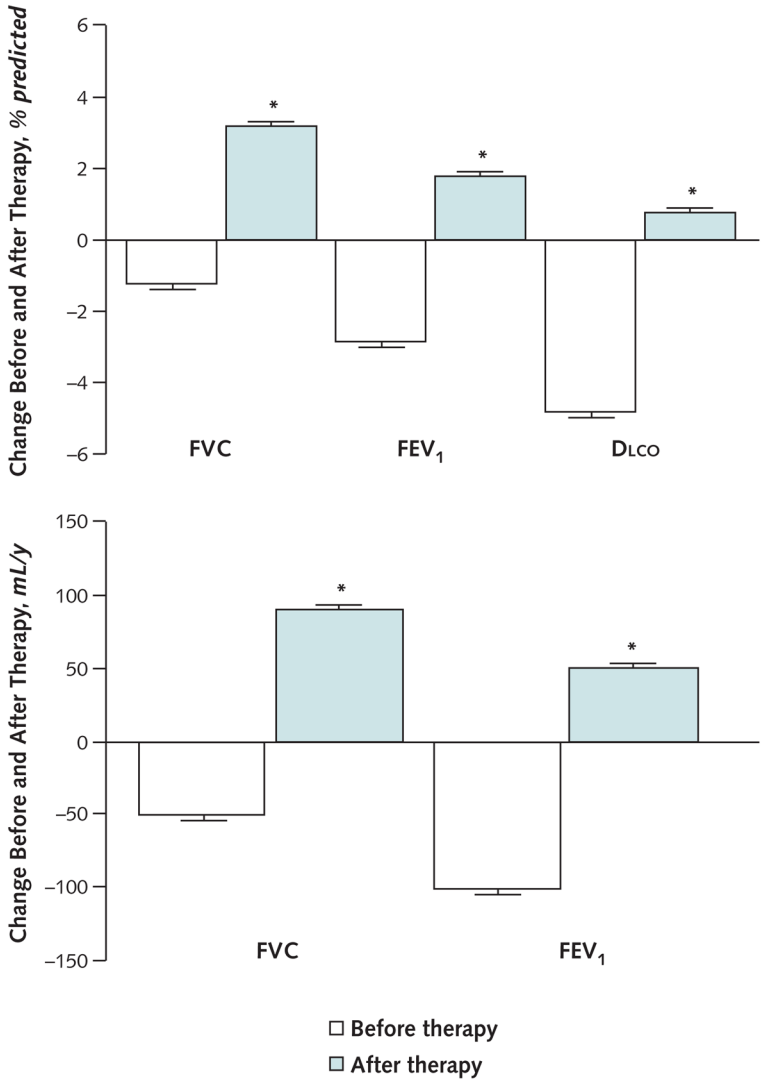


Figure 2. Mean annual changes in FVC, FEV_1, and D_{LCO} before and after sirolimus therapy in patients with lymphangioleiomyomatosis

Data were obtained by using mixed-effects models. During sirolimus therapy, the FVC, FEV_1, and $_{DLCO}$ increased instead of decreasing. D_{LCO} = diffusing capacity of the lung for carbon monoxide.

* Eighteen patients were included in these analyses because 1 patient could not undergo pulmonary function tests.

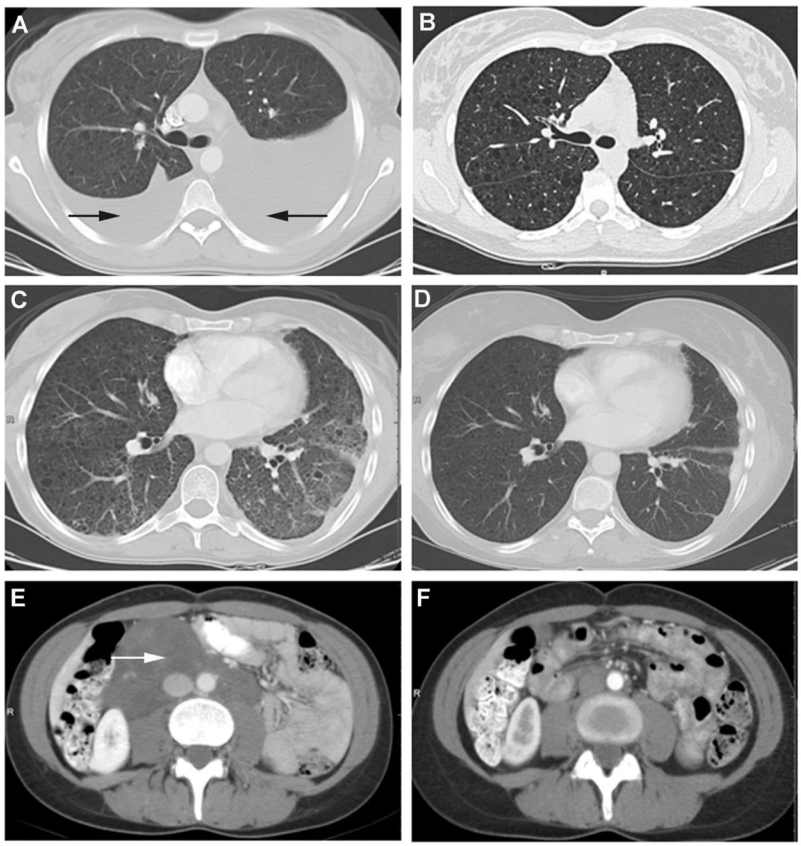
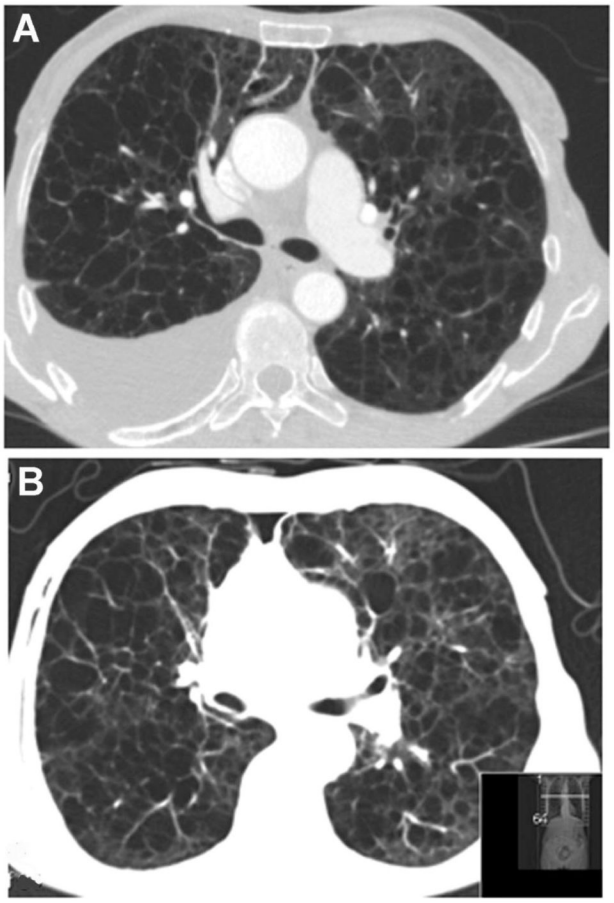


Figure 3. CT scans in 3 patients with lymphangioleiomyomatosis before and after sirolimus therapy

CT = computed tomography. **A**. CT scan of a 29-year-old woman with bilateral chylothorax (*black arrows*). **B.** Repeated CT scan of the same patient 30 months after starting sirolimus therapy that shows complete resolution of the pleural effusions. **C.** CT scan of a 45-year-old woman with bilateral lung infiltrates. **D**. Repeated CT scan of the same patient performed after 2.5 years of sirolimus therapy that shows complete clearing of the infiltrates; her lung function also had improved. **E.** CT scan of a 39-year-old woman with a large lymphangioleiomyoma (*white arrow*). **F.** Repeated CT scan of the same patient after 11 months of sirolimus therapy that shows the lymphangioleiomyoma completely resolved.



Appendix Figure. Follow-up Visit CT scan in a patient with lymphangioleiomyomatosis with pleural effusion requiring persistent drainage

CT = computed tomography. **A.** CT scan of a 62-year-old woman who had undergone unsuccessful chemical pleurodesis and required daily drainage of substantial amounts of pleural fluid. **B.** Repeated CT scan after 6 months of sirolimus therapy showing nearly complete resolution of pleural effusion.

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Table 1

Changes in Chylous Effusions and Lymphangioleiomyomas During Treatment With Sirolimus

Patient	Pleural Effusions	Ascites	Lymphangioleiomyomas	Mean Serum Sirolimus Level (±SE), *ng/mL*	Response to Therapy	Adverse Events
1	No	No	No	7.7 ± 1.3	No lymphatic involvement	Hypertension, acne
2	No	No	Yes	9.7 ± 1.6	Reduction in size of lymphangioleiomyomas	None
3	Yes	Yes	Yes	4.6 ± 0.7	Resolution of effusions and lymphangioleiomyomas	Oral ulcers, diarrhea, hyperlipidemia, acne, hypertension
4	No	No	No	7.0 ± 0.3	No lymphatic involvement	None
5	No	No	No	7.4 ± 1.8	No lymphatic involvement	Oral ulcers, rash, hyperlipidemia, diarrhea, hypertension, neutropenia
6	No	Yes	Yes	7.7 ± 0.6	Resolution of lymphangioleiomyomas	Oral ulcers, acne, hyperlipidemia, rash
7	Yes	No	Yes	10.4 ± 1.6	Resolution of effusions and lymphangioleiomyomas	Oral ulcers
8	No	No	No	5.7 ± 0.8	No lymphatic involvement	Hyperlipidemia, acne
9	Yes	No	Yes	5.8 ± 0.2	Resolution of effusions and lymphangioleiomyomas	None
10	No	No	No	11.3 ± 0.3	No lymphatic involvement	Hyperlipidemia, acne, diarrhea
11	Yes	No	Yes	5.8 ± 0.5	Decrease in size of effusions; resolution of lymphangioleiomyomas	Hyperlipidemia, bruising
12	Yes	No	Yes	9.4 ± 1.9	Resolution of effusions and lymphangioleiomyomas	None
13	Yes	No	Yes	7.4 ± 1.6	Resolution of effusions and lymphangioleiomyomas	Oral ulcers, diarrhea, hyperlipidemia, irregular menses
14	Yes	Yes	Yes	6.2 ± 1.8	Resolution of effusions and lymphangioleiomyomas; discontinuation of pleural drainage	Oral ulcers, acne
15	No	No	No	6.6 ± 1.3	No lymphatic involvement	Acne of the face and edema of the legs
16	Yes	Yes	No	5.6 ± 0.3	Resolution of effusions	Oral ulcers, hyperlipidemia
17	Yes	Yes	Yes	9.9 ± 0.6	Resolution of effusions	Oral ulcers, menorrhagia
18	Yes	Yes	No	5.0 ± 0.2	Resolution of effusions	Skin infection
19	Yes	Yes	Yes	7.7 ± 1.7	Marked resolution of effusions and lymphangioleiomyomas; discontinuation of pleural drainage	None

Appendix Table

Age and Pulmonary Function Test Results in Patients With Lymphangioleiomyomatosis Before and After Sirolimus Therapy*

Characteristic	First Test at Enrollment in Natural History Study	Just Before Sirolimus Therapy	At Most Recent Follow-up Visit
Mean age (SD), *y*	39.6 (9.8)	41.0 (9.0)	43.6 (8.8)
Mean time before and after therapy (SD), *y*	−2.6 (1.3)	0	2.6 (1.1)
Median pulmonary function study results (IQR)			
TLC, *% predicted*	94 (84–103)	90 (69–96)	96 (86–107)
FRC, *% predicted*	102 (92–110)	100 (78–108)	109 (90–112)
RV, *% predicted*	103 (90–118)	99 (86–130)	99 (86–130)
RV–TLC ratio, *%*	35 (33–41)	38 (32–46)	34 (30–41)
FVC, *% predicted*	95 (77–100)	79 (61–95)	92 (69–113)
FEV_1, *% predicted*	81 (59–98)	61 (40–81)	70 (42–87)
FEV_1–FVC ratio, *%*	71 (60–80)	58 (46–72)	54 (39–73)
D_{LCO}, *% predicted*	58 (47–71)	41 (29–47)	43 (30–52)

D_{LCO} = diffusing capacity of the lung for carbon monoxide; FRC = functional residual capacity; IQR = interquartile range; RV = residual volume; TLC = total lung capacity.

*Eighteen patients were included in these analyses because 1 patient could not undergo pulmonary function tests.