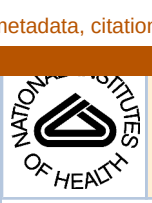

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Effect of a Gonadotrophin-Releasing Hormone Analogue on Lung Function in Lymphangioleiomyomatosis

Sergio Harari, MD, **Roberto Cassandro, MD**, **Jacopo Chiodini, MD**, **Angelo M. Taveira-DaSilva, MD, PhD**, and **Joel Moss, MD, PhD**

Unità di Pneumologia e Terapia Semi-Intensiva Respiratoria (Drs. Harari and Cassandro), Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare, and Unidade Operativa di Endocrinologia (Dr. Chiodini), Ospedale San Giuseppe AFAR, Milan, Italy; and Translational Medicine Branch (Drs. Taveira-DaSilva and Moss), National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD.

Abstract

Background—Lymphangioleiomyomatosis (LAM), a multisystem disease occurring primarily in women, is characterized by cystic lung destruction, and kidney and lymphatic tumors, caused by the proliferation of abnormal-appearing cells (*ie*, LAM cells) with a smooth muscle cell phenotype that express melanoma antigens and are capable of metastasizing. Estrogen receptors are present in LAM cells, and this finding, along with reports of disease progression during pregnancy or following exogenous estrogen administration, suggest the involvement of estrogens in the pathogenesis of LAM. Consequently, antiestrogen therapies have been employed in treatment. The goal of this prospective study was to evaluate the efficacy of triptorelin, a gonadotrophin-releasing hormone analogue, in 11 premenopausal women with LAM.

Methods—Patients were evaluated at baseline and every 3 to 6 months thereafter, for a total of 36 months. Hormonal assays, pulmonary function tests, 6-min walk tests, high-resolution CT scans of the chest, and bone mineral density studies were performed.

Results—Gonadal suppression was achieved in all patients. Overall, a significant decline in lung function was observed; two patients underwent lung transplantation 1 year after study enrollment, and another patient was lost to follow-up. Treatment with triptorelin was associated with a decline in bone mineral density.

Conclusions—Triptorelin appears not to prevent a decline in lung function in patients with LAM. Its use, however, may be associated with the loss of bone mineral density.

Keywords

gonadotrophin-releasing hormone analogues; lung function; lymphangioleiomyomatosis; osteoporosis; triptorelin

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Lymphangioleiomyomatosis (LAM), a multisystem disease primarily affecting women, is characterized by the proliferation of abnormal-appearing cells (*ie*, LAM cells) that have a smooth muscle cell phenotype expressing melanoma antigens and are capable of metastasizing, leading to cystic destruction of the lungs, infiltration of the axial lymphatics (*eg*,

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Correspondence to: Angelo M. Taveira-DaSilva, MD, PhD, Translational Medicine Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Building 10, Room 6D05, MSC 1590, Bethesda, MD 20892-1590; dasilvaa@nhlbi. nih.gov .

lymphangioleiomyomas), and abdominal tumors (*eg*, angiomyolipomas).[1–3] LAM occurs sporadically or in association with tuberous sclerosis complex (TSC), an autosomal-dominant syndrome that is characterized by mental retardation, seizures, hamartomatous growths,[4] and mutations in the tumor suppressor genes *TSC1* and *TSC2*. These genes have been implicated in the pathogenesis of sporadic LAM, as mutations and the loss of heterozygosity in the *TSC2* gene have been detected in LAM cells of patients without evidence of TSC.[5] The *TSC1* gene encodes hamartin, and the *TSC2* gene encodes tuberin, two proteins with roles in cell growth, proliferation, and cytoskeletal organization.[6]

Patients with LAM may present with progressive breathlessness, pneumothorax, chylothorax, asthmalike symptoms, or hemorrhage within angiomyolipomas.[1–3] CT scans show numerous thin-walled cysts throughout the lungs, abdominal angiomyolipomas, and lymphangioleiomyomas.[7] Pulmonary function test results may show a reduction in flow rates and diffusing capacity of the lung for carbon monoxide (D_{LCO}).[2] Exercise testing may reveal gas-exchange abnormalities, ventilatory limitation, and hypoxemia, which may occur with near-normal lung function.[8]

The preferential occurrence of LAM in women during their reproductive years,[1,2] the presence of progesterone and estrogen receptors in LAM cells,[9] and reports of deterioration of lung disease during pregnancy[10,11] or following the administration of estrogens,[12,13] are consistent with hormonal involvement in the pathogenesis of the disease. Treatments for LAM have consisted mostly of oophorectomy and hormonal manipulations with progesterone or other agents.[14–21] In a retrospective analysis[22] of lung function decline in 275 LAM patients, however, no evidence was found of a beneficial effect of progesterone treatment.

The efficacy of gonadotrophin-releasing hormone (Gn-RH) agonists and analogues in the treatment of LAM has also been the subject of several reports.[23–25] Gn-RH analogues, such as goserelin and triptorelin, are long-acting synthetic compounds that have high affinity for neurohormonal receptors and a longer half-life than Gn-RH agonists.[26] The long-term and continuous administration of Gn-RH analogues causes a sustained decrease in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion and a depression of gonadal function.[26] Prior experience with the treatment of LAM with Gn-RH analogues, consisting of case reports,[23,25] have yielded conflicting results. However, Medeiros et al,[27] in a retrospective analysis of lung function decline in patients with LAM, found that patients treated with goserelin had no decline in lung function, whereas those patients treated with progesterone continued to experience a decline. The goal of our study was to evaluate, prospectively, the effect of treatment with triptorelin in premenopausal patients with LAM.

Materials and Methods

Study Population

This study evaluated the response to treatment with triptorelin, a synthetic analogue of Gn-RH (11.25 mg IM every 3 months) in 11 premenopausal LAM patients. Informed consent was obtained from all patients, and the protocol was approved by the San Giuseppe Hospital Institutional Review Board.

Study Design

Patients were evaluated at baseline, and at 3, 6, 12, 18, 24, and 36 months after initiating therapy. Routine blood testing and hormonal assays (*ie*, for FSH, LH, 17 β-estradiol, and total testosterone) were performed every 6 months. Pulmonary function tests, arterial blood gas measurements, 6-min walk tests (6MWT), and high-resolution CT (HRCT) scans were performed once a year. Bone densitometry of the lumbar spine and femoral neck was measured

at baseline and at 18 and 36 months after study enrollment. The primary end point of the study was the decline in FEV_1. Secondary end points were the 6MWT distance and changes in HRCT lung scan findings.

Pulmonary Function Tests

Lung volumes, flow rates, and single-breath D_{LCO} were measured ($\dot{V}_{max}$ 229; SensorMedics; Yorba Linda, CA), according to American Thoracic Society recommendations.[28,29] Four of the 11 patients had a history of a positive response to bronchodilators. All spirometric data reported here are from prebronchodilator studies.

Arterial Blood Gases

Arterial blood samples were drawn from the radial artery of resting patients breathing room air. Blood specimens were placed on ice, and tests were run immediately.

6MWT and Arterial Pulse Oximetry

6MWTs were performed using the protocol of Sciurba and Slivka.[30] Patients were instructed to walk as fast as possible for 6 min, while being encouraged using set phrases every 30 s.[31] Two patients were exercised while receiving supplemental oxygen. For all patients, the test was stopped if oxygen saturation dropped below 86%.[32]

Radiographic Assessment

HRCT scans of the chest were obtained (Tomoscan AV scanner; Philips; Amsterdam, the Netherlands) at 10-mm intervals using 10-mm collimation during breath-holding at the end of inspiration.[33] A quantitative HRCT scan analysis was performed using the "density mask" software on images from three lung zones (*ie*, aortic arch, left lower lobe bronchus origin, and 2 cm above the diaphragmatic muscle level) at end expiration, as previously reported.[33] This procedure identified areas of airtrapping. The percentage of airtrapping at the three standard lung zones was calculated, and values were averaged; a final value was provided that reflected the amount of airtrapping in both lungs.[33]

Bone Densitometry

The bone mineral density of the lumbar spine (anterior and lateral) and proximal femur was assessed by dual-energy radiograph absorptiometry (QDR-4500; Hologic; Bedford, MA).[34] The z scores were derived from age-matched reference values.[34]

Statistical Analysis

The yearly rate of decline in lung function was calculated from a linear regression using FEV_1 and D_{LCO} as the response variables and the time of each test as the independent variable, considering the first test as time zero.[22] The Student *t* test was employed to compare data sets. Analysis of variance (ANOVA) for repeated measurements was employed to evaluate changes in physiologic and quantitative HRCT scan data. All reported p values are two-sided. All data are shown as the mean ± SD.

Results

Characteristics of the Patients

Of the 11 patients (mean age, 37 ± 7 years; age range, 24 to 49 years), 9 had a histologically proven diagnosis of LAM, and 2 patients exhibited clinical and radiographic features consistent with LAM. Radiographic features consisted of the presence of thin-walled cysts scattered throughout the lungs combined with abdominal angiomyolipomas and/or

lymphangioleiomyomas.[2] Three patients were ex-smokers; the remaining patients were nonsmokers. One patient had LAM/TSC. Four patients had renal angiomyolipomas. Sequential preenrollment pulmonary function data were available in three patients.

Therapy was initiated in all 11 patients; one patient failed to complete the study because of drug-related adverse events. During the study, two patients underwent lung transplantation. These patients continued to receive the study drug for only 1 year. For these two patients, the data included in the analysis refer to pretransplant studies. Pneumothorax did not develop in any patient while under treatment; two patients had subsequent episodes of pneumothorax.

Evidence for Gonadal Suppression: Adverse Effects

Treatment with triptorelin induced hypogonadotrophic hypogonadism (Table 1). Five patients reported the following adverse events: four patients had flushing; two patients had arthralgias and paresthesias; and two patients complained of fatigue and dizziness. Anxiety and depressive symptoms developed in one patient. All patients, except those who underwent lung transplantation and remained enrolled in the study for only 1 year, completed 3 years of treatment.

Pulmonary Function, Arterial Blood Gas Measurements, and 6MWT Results

Table 2 shows initial pulmonary function test results, Pao_2 measurements, and 6MWT findings for every year until the completion of the study. ANOVA showed that the Pao_2 at the third year of the study was significantly lower than that at baseline ($p < 0.01$) and at the first year of the study ($p < 0.05$). ANOVA showed no significant changes in lung function and 6MWT results. This could be due to the fact that the number of patients remaining in the study decreased after the first year and also because there is a large variance in lung function parameters among the study subjects. However, at the end of the study, all but one patient had experienced declines in FEV_1 (Fig 1). Moreover, all nine patients who were able to perform the D_{LCO} test had a decline in function (Fig 2). Table 3 shows that, when compared to two previous retrospective studies,[21,22] the mean yearly declines in FEV_1 (156 ± 184 mL; 4.9 ± 5.9% predicted) and D_{LCO} (1.3 ± 0.4 mL/min/mm Hg; 4.9 ± 5.0% predicted) were greater. One of the 10 patients showed improvement in FEV_1 and 6MWT distance during the 3 years of the study; in this patient, FEV_1 increased by 360 mL, and the 6MWT distance increased by 100 m. However, this patient experienced a large yearly decline in D_{LCO} (1.9 mL/min/mm Hg; 5.9% predicted).

Pre-study enrollment pulmonary function data were available only in three patients. The rate of decline of FEV_1 was unchanged in one patient; in the other two patients, the rate of FEV_1 decline increased after initiating therapy with triptorelin. In one patient, the yearly rate of change in FEV_1 went from −60 to −137 mL/year, and in the second patient went from +10 to −161 mL/year.

Quantitative HRCT Scans

Table 4 shows the mean percentage of airtrapping for the three standard lung zones at baseline and at subsequent visits. An increase in values indicates the presence of a greater degree of airtrapping, which presumably corresponds to an increase in the number and/or size of the lung cysts. The percentage of airtrapping tended to increase in all but three patients (Table 4). For the whole group, however, the change in the percentage of airtrapping was not statistically significant.

Bone Mineral Density

Initial bone mineral density was normal in all patients. The mean lumbar spine and femoral neck z scores were 1.328 ± 0.144 and 1.276 ± 0.248, respectively. At 36 months, the mean

lumbar spine and femoral neck z scores had declined to 0.421 ± 1.268 (p = 0.04) and 0.524 ± 0.744 (p = 0.016), respectively. The yearly rate of decline in z scores, expressed as a percentage of the initial values, was 22 ± 26% and 24 ± 26%, respectively. At the conclusion of the study, two patients showed evidence of lumbar spine osteopenia.

Discussion

The goal of this study was to evaluate the effect of treatment with triptorelin, a Gn-RH analogue, on lung function in patients with LAM. Although triptorelin was effective in suppressing ovarian function, all but 1 of the 10 patients who completed the study experienced a decline in FEV_1; a reduction in D_{LCO} was observed in all patients. In two cases, an accelerated loss of lung function resulted in lung transplantation. Only one patient showed improvement in FEV_1 and 6MWT distance, despite deterioration in D_{LCO}. The mean yearly rates of decline in FEV_1 and D_{LCO} are higher than those observed by Johnson and Tattersfield[21] and Taveira-DaSilva et al.[22] However, the rates of lung function decline in LAM patients are highly variable; consequently, when relatively low numbers of patients are studied, the SD of the average declines in FEV_1 or D_{LCO} are large. As shown in Table 3 in the study by Johnson and Tattersfield,[21] the mean rate of change in FEV_1 was 108 ± 101 mL/year. In our retrospective study of 275 patients, we found a mean rate of FEV1 decline of 75 ± 17 mL/year. It should be noted that the 10 patients who are the subject of the current report had lower initial lung function than the subjects of our retrospective study.[22] This may explain why their decline in FEV was higher.[22] 1 Indeed, the decline in FEV_1 was lower in 5 of the 10 patients who had milder disease than in the remaining patients (93 ± 54 vs 220 ± 102 mL/year, respectively). Because of the small numbers of patients, the difference was not statistically significant. Interestingly, the yearly rates of D_{LCO} decline were similar for the same two subgroups of patients (1.24 ± 0.23 vs 1.33 ± 0.99 mL/min/mm Hg, respectively). Although it is possible that the milder disease subgroup had a more benign disease course, their rate of FEV_1 decline is comparable to that reported by Johnson and Tattersfield.[21] Consequently, we believe that our cohort as a whole is representative of a LAM population, and treatment with a Gn-RH analogue failed to affect disease progression. Based on the current study, we cannot say that triptorelin is actually harmful.

Adverse effects of triptorelin such as flushing, arthralgia, paresthesias, fatigue, dizziness, anxiety and depressive symptoms were observed, but only 1 of the 11 initial patients failed to complete the study because of adverse events. In addition, a decline in bone mineral density was observed after the administration of triptorelin. In a prior study,[34] LAM patients had a high frequency of abnormal bone density, which did not appear to be related to progesterone therapy.

Antiestrogen therapies have been used in the treatment of LAM, but controlled trials[23–25] have not been performed. Prior experience with Gn-RH analogues, consisting of case reports or retrospective studies comprising few patients, is conflicting. Our prospective study shows that treatment with a Gn-RH analogue did not affect disease progression. Our observations however, are based only on a group 10 patients, which may have excluded patients who are more likely to respond to treatment; the study was not randomized, and disease severity varied widely among patients.

Nobody expects hormonal therapy to cause the regression of cystic lung lesions. However, such therapy, if effective, may arrest LAM cell growth, and decrease the size of angiomyolipomas, lymphangioleiomyomas, and chylous effusions. It is accepted that estrogens in some way facilitate the occurrence of LAM, making it almost exclusively a disease of women. In addition, there is evidence that endogenous or exogenous estrogens (*eg*, from pregnancy or estrogen-containing contraceptives) worsen LAM,[10–13] but the reverse may not

be true. That is, oophorectomy, antiestrogen therapy, or gonadotrophin analogues may not improve disease progression in patients with LAM.

Our extensive retrospective study,[22] including patients of all ages and grades of disease severity, showed that those patients with more severe disease were more likely to be treated with progesterone and those treated orally faired worse than groups given IM-administered progesterone or no progesterone. The current study shows that the suppression of ovarian function does not affect disease progression. This is true even in the subgroup of patients with milder disease in whom we observed greater rates of decline in FEV_1 and D_{LCO} than those seen in prior studies.[21,22] In conclusion, our findings do not support a role for triptorelin, or similar types of drugs, in the treatment of LAM. Of importance, this therapy appears to be associated with adverse effects, especially bone mineral loss. We believe that oophorectomy or antiestrogen therapy with progesterone or agents that suppress ovarian function does not prevent or diminish lung disease progression in patients with LAM.

A possible beneficial effect of Gn-RH analogues in the therapy of selected LAM patients, such as those with chylous effusions and lymphangioleiomyomas, cannot be completely excluded. There are anecdotal reports of patients with chylous effusions whose conditions have "improved" after treatment with progesterone and/or oophorectomy. Indeed, for lack of a better treatment, antiestrogen therapy is occasionally prescribed for such patients. Our negative findings, however, suggest that alternative therapeutic approaches rather than hormonal therapies need to be sought for the treatment of LAM.

Acknowledgments

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Abbreviations

ANOVA	analysis of variance
D_{LCO}	diffusing capacity of the lung for carbon monoxide
FSH	follicle-stimulating hormone
Gn-RH	gonadotrophin-releasing hormone
HRCT	high-resolution CT
LAM	lymphangioleiomyomatosis
LH	luteinizing hormone
6MWT	6-min walk test
TSC	tuberous sclerosis complex

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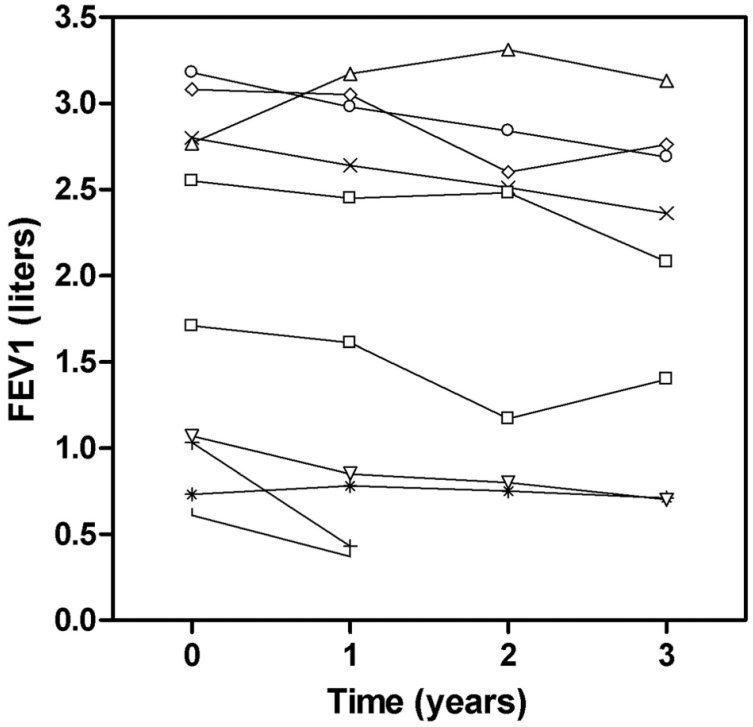

Figure 1.
Changes in FEV_1 in 10 patients with LAM who were treated with triptorelin.

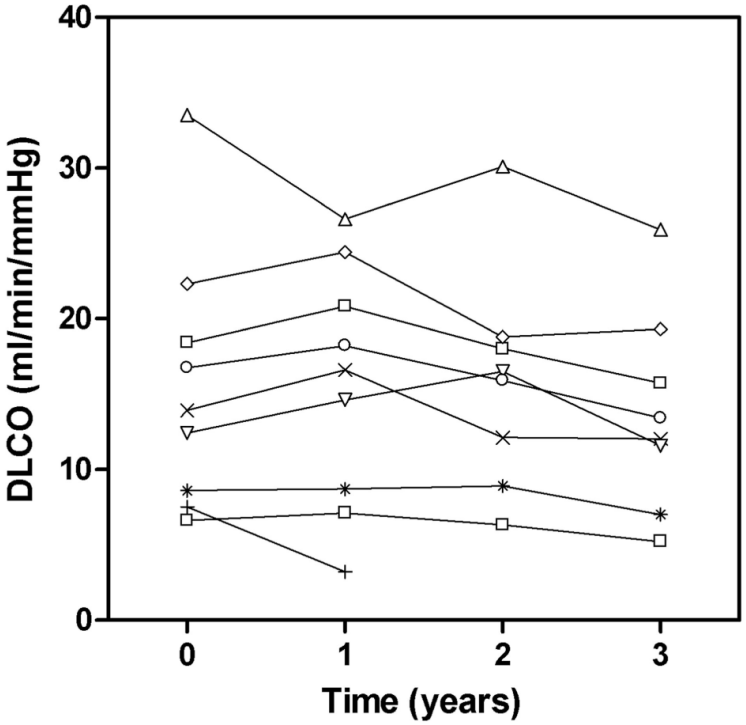

Figure 2.
Changes in D_{LCO} in nine patients with LAM who were treated with triptorelin.

Table 1

Hormonal Levels in 10 Patients Treated With Triptorelin*

Hormones	Initial (n = 10)	18 mo (n = 8)	36 mo (n = 8)
FSH,† mIU/mL	5.4 ± 3.5	4.2 ± 1.8	4.1 ± 2.4
LH,‡ mIU/mL	1.8 ± 3.3	0.4 ± 0.2	0.21 ± 0.19
17 β-estradiol,§ pg/mL	32.6 ± 23.1	19.5 ± 3.8	1.5 ± 2.2

*Values are given as the mean ± SD.

†Normal values, 2.8 to 11.3 mIU/mL.

‡Normal values, 1.6 to 8.3 mIU/mL.

§Normal values, 26 to 165 pg/mL.

Table 2

Pulmonary Function and Exercise Data Before and During Triptorelin Therapy in 10 Patients With LAM*

Variables	Initial (n = 10)	1 yr (n = 10)	2 yr (n = 8)	3 yr (n = 8)
FVC				
L	2.9 ± 0.8	2.9 ± 1.0	3.2 ± 0.6	3.0 ± 0.8
% predicted	75 ± 34	83 ± 28	93 ± 13	90 ± 18
FEV_1				
L	1.9 ± 1.0	1.8 ± 1.1	2.0 ± 0.9	1.9 ± 0.9
% predicted	64 ± 31	60 ± 34	68 ± 27	65 ± 26
FEV_1/FVC ratio, %	62 ± 23	57 ± 23	61 ± 23	60 ± 17
TLC				
L	5.0 ± 0.4	4.6 ± 0.4	4.8 ± 0.3	4.8 ± 0.3
% predicted	99 ± 13	95 ± 8	96 ± 10	96 ± 13
FRC				
L	2.9 ± 0.5	2.8 ± 0.5	3.0 ± 0.4	3.1 ± 0.7
% predicted	107 ± 19	103 ± 19	113 ± 20	113 ± 27
RV				
L	1.8 ± 0.7	1.5 ± 0.6	1.6 ± 0.6	1.8 ± 0.8
% predicted	121 ± 46	98 ± 36	100 ± 37	110 ± 53
RV/TLC ratio,%	36 ± 13	33 ± 15	33 ± 12	36 ± 17
D_{LCO}				
mL/min/mmHg	15.5 ± 8.5	15.0 ± 8.0	15.8 ± 7.2	13.7 ± 6.6
% predicted	58 ± 28	55 ± 27	59 ± 24	51 ± 21
Pao_2, mm Hg	83 ± 8†	81 ± 9†	80 ± 10	75 ± 12
6MWT distance, m	458 ± 73	433 ± 179	459 ± 77	487 ± 95

*Values are given as the mean ± SD. FRC = functional residual capacity; RV = residual volume; TLC = total lung capacity.

†Significantly different from value at 3 years post-study enrollment by ANOVA ($p < 0.05$).

Table 3

Comparison Between Rates of Lung Function Decline in Study Subjects and Historical Control Subjects*

Patients, No.	Initial FEV_1, % predicted	Change FEV_1/yr, mL (% Predicted)	Initial D_{LCO}, % Predicted	Change in D_{LCO}/yr, mL/min/mm Hg (% Predicted)	Years
32†	Not given	−108 ± 101	Not given	−0.905 ± 1.54	3–3.5
275‡	75 ± 22	−75 ± 17 (−1.7 ± 6.3)	72 ± 26	−0.69 ± 1.2 (−2.4 ± 6.2)	4
10§	64 ± 31	−156 ± 184 (−4.9 ± 5.9)	58 ± 28	−1.3 ± 0.4 (−4.9 ± 5.0)	1–3

*Values are given as the mean ± SD.

†From Johnson and Tattersfield.[21]

‡From Taveira-DaSilva et al.[22]

§From the current study.

Table 4

Average of Percent Lung Air-Trapping at Three Lung Zones Measured by Quantitative High-Resolution CT Scans at Baseline and Subsequent Visits in 10 Patients With LAM*

Patient No.	Initial	1 yr	2 yr	3 yr
1†	38 ± 6	52 ± 5		
2	47 ± 4	49 ± 3	47 ± 3	55 ± 4
3†	47 ± 11	57 ± 10		
4	7 ± 2	9 ± 2	14 ± 4	11 ± 2
5	39 ± 4	55 ± 5	39 ± 4	30 ± 9
6	17 ± 3	11 ± 3	13 ± 2	34 ± 16
7	12 ± 2	10 ± 3	7 ± 1	16 ± 3
8	32 ± 9	39 ± 8	40 ± 11	38 ± 11
9	5 ± 1	4 ± 1	5 ± 1	4 ± 2
10	9 ± 2	5 ± 1	12 ± 2	10 ± 1

*Values are given as the mean ± SD.

†Patients underwent lung transplantation.