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A 2-year, single arm, open-label, investigator-initiated clinical trial (the MLSTS trial) was conducted in 63 Japanese women with lymphangioleiomyomatosis (LAM) at 9 sites in Japan to determine the durability and tolerability of longer-term sirolimus treatment than the MILES trial. As compared with the MILES trial in which LAM patients with FEV1 < 70% predicted participated, mild cases with FEV1 ≥70% predicted were enrolled together with those with FEV1 < 70% predicted. Fifty-two subjects (82.5%) completed the trial with the meant drug compliance of more than 80% during the study. Two-year treatment with sirolimus was associated with 1,540 adverse events (AEs) that was well known to be related with mTOR inhibitors. Twenty-seven severe AEs including reversible sirolimus-induced pneumonitis were reported. New hypercholesterolemia occurred in 30 patients, microcythemia in 10 patients, body weight loss in 33 patients, and increased blood pressure that required treatment in 5 patients. Pulmonary function (FEV1 and FVC) and quality of life did not improved, but were stable in the overall study cohort during the 2-year study period.


Both the American Thoracic Society and Japanese Respiratory Society collaborated to provide recommendations for the diagnosis and treatment of lymphangioleiomyomatosis (LAM). Systematic reviews were performed to summarize evidence pertinent to 4 clinical questions selected; Question 1: Should patients with LAM be treated with sirolimus?, Question 2: Should patients with LAM be treated with doxycycline?, Question 3: Should patients with LAM be treated with hormonal therapy?, and Question 4: Should serum VEGF-D be used to confirm the diagnosis of LAM in women with compatible cystic change on computed tomography of the chest? The GRADE approach (Grading of Recommendations. Assessment, Development, and Evaluation) were utilized to describe evidence-based recommendations for those 4 clinical questions. Since LAM is a rare lung disease with limited high quality evidence, frequent reassessment and updating will be needed.

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A total pleural covering for lymphangioleiomyomatosis prevents pneumothorax recurrence.


Spontaneous pneumothorax is a major and frequently recurrent complication of lymphangioleiomyomatosis (LAM). Despite the customary use of pleurodesis to manage pneumothorax, the recurrence rate remains high, and accompanying pleural adhesions cause serious bleeding during subsequent lung transplantation. Therefore, the author’s group developed a technique of total pleural covering (TPC) for LAM to wrap the entire visceral pleura with sheets of oxidized regenerated cellulose (ORC) mesh, thereby reinforcing the affected visceral pleura and preventing recurrence. They applied TPC to 43 LAM patients (54 hemithoraces), 11 of whom required TPC bilaterally, from January 2003 to August 2014. Pneumothorax recurred in 14 hemithoraces (25.9%) from 11 patients (25.6%) after TPC. Kaplan-Meier estimates of recurrence-free hemithorax were 80.8% at 2.5 years, 71.7% at 5 years, 71.7% at 7.5 years, and 61.4% at 9 years. The recurrence-free probability was significantly better when 10 or more sheets of ORC mesh were utilized for TPC (P = 0.0018). TPC significantly reduced the frequency of pneumothorax: 0.544 ± 0.606 episode/month (mean ± SD) before TPC vs. 0.008 ± 0.019 after TPC (P<0.0001). Grade IIIa postoperative complications were found in 13 TPC surgeries (24.1%). Accordingly, TPC successfully prevented the recurrence of pneumothorax in LAM, was minimally invasive and rarely caused restrictive ventilatory impairment.

Incidence of Pneumothorax in Patients With Lymphangioleiomyomatosis Undergoing Pulmonary Function and Exercise Testing.


The authors reported the incidence of pneumothorax associated with pulmonary function or exercise testing in patients with lymphangioleiomyomatosis (LAM) during admissions to the National Institutes of Health Clinical Research Center between 1995 and 2015. A total of 691 patients underwent 4,523 pulmonary function tests and 1,900 exercise tests. Only 3 patients developed pneumothorax after pulmonary function tests and/or exercise tests. The incidence of pneumothorax associated with lung function testing was 0.02 to 0.04 of 100 tests whereas the one associated with undergoing exercise testing was 0.05 to 0.10 of 100 tests. The risk of pneumothorax associated with these testing in LAM, one of the diseases with frequent occurrence of pneumothorax, is very low.
Isolation of individual cellular components from lung tissues of patients with lymphangioleiomyomatosis.

http://ajplung.physiology.org/content/310/10/L899.long

A fluorescence-activated cell sorting (FACS)-based method for the direct isolation of LAM cells and other various cellular components from LAM-affected lung tissue was reported. LAM cells were defined as HMB45-positive cells with tuberous sclerosis complex (TSC) 2 loss of heterozygosity (LOH). From cell suspension prepared from LAM lungs, the mesenchymal cell population of CD45(-)/EpCAM(-)/podoplanin(-/low)/ CD90(+)/CD34(-) included HBM45(+)/TSC2 LOH(+) LAM cells. Isolated cells were viable and subsequently amenable to cell culture.

Bronchial involvement in advanced stage lymphangioleiomyomatosis: histopathologic and molecular analyses.


The results of histopathologic examinations of the entire airway using explanted lung tissues from 30 LAM patients. Airflow obstruction that is commonly observed in LAM has been attributed to narrowing of peripheral airways, but the authors performed a thorough histologic analysis with a special emphasis on the bronchi because surgical pathologic specimen of peripheral lung tissue have precluded the analysis of central airways. The authors found that patients with advanced LAM commonly have bronchi involved by the proliferation of both LAM cells and lymphatics and that chronic inflammation complicated their disease. Furthermore, the up-regulation of hypoxia-inducible factor 1α, a common event in mTORC1-driven tumor cells, does not occur in LAM cells and plays no role in VEGF-D expression in LAM cells.

Pulmonary rehabilitation in lymphangioleiomyomatosis: a controlled clinical trial.

http://erj.ersjournals.com/content/47/5/1452.long

The authors evaluated the safety and efficacy of pulmonary rehabilitation in patients with lymphangioleiomyomatosis (LAM) by a controlled clinical trial included 40 patients with LAM and a low physical activity level. The pulmonary rehabilitation (PR) programme comprised 24 aerobic and muscle strength training sessions and education. The authors demonstrated that their PR programme significantly improved endurance time, SGRQ, 6MWD, dyspnea, peak VO2, daily physical activity and muscle strength. No serious adverse events were observed.
Wild type mesenchymal cells contribute to the lung pathology of lymphangioleiomyomatosis.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4433241/

By the immunohistochemical examinations, a mouse model, and in vitro cell co-culture system, the authors demonstrated that LAM nodules are heterogeneous structures containing mesenchymal cells (fibroblast-like cells) that may provide a permissive environment for LAM cell growth. They found many mesenchymal cells positive for various fibroblast markers. Using a mouse model of LAM, they also demonstrated that tuberin-positive host derived cells were also present within lung nodules of xenografted TSC2 null cells. In vitro cell co-culture system, they found that LAM 621-101 cell-derived CXCL12 have some role in chemotaxis of fibroblasts toward LAM cells. Their findings were quite analogous to cancer lesions consisting of cancer cells and cancer-associated fibroblasts.

Genetic heterogeneity of circulating cells from patients with lymphangioleiomyomatosis with and without lung transplantation.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4407489/

The authors group has presented the data indicating clonal heterogeneity of LAM cells in blood and urine. Although LAM is considered to be a low-grade neoplasm, their findings suggest that LAM also shows genetic heterogeneity, whether due to multiclonal origin or genetic instability overtime, like many human cancers. They examined blood and urine samples collected from 65 LAM patients. Both CD45-/CD235a+ and CD45-/CD235a+ cell populations from blood and CD44v6+/CD9+ cells from urine were examined for TSC2 LOH. About 25% of patients who had TSC2 LOH in both CD45-/CD235a+ and CD45-/CD235a+ cell populations had different LOH patterns, suggesting that a single patient may have different clones of LAM cells. When LOH pattern was compared between blood and urine, 33% of patients showed different pattern of LOH. Additionally, three LAM patients showed different patterns of allelic loss in blood subpopulations or blood vs. urine overtime.
Sustained effects of sirolimus on lung function and cystic lung lesions in lymphangioleiomyomatosis.

https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/25329516/

The authors reported the sustained effects of sirolimus on lung function in patients with LAM. The study population consisted of 38 LAM patients, and 12 patients among them followed for 5 years. Yearly declines in FEV1 % pred (-2.3±0.1 vs. 1.0±0.3%; P<0.001) and DLco %pred (-2.6±0.1 vs. 0.9±0.2% pred; P<0.001) reduced significantly, but no change in pulmonary cysts was noted. In 12 patients who were followed for 5 years, a significant reduction in rates of yearly decline in FEV1 (-1.4±0.2 vs. 0.3±0.4% pred; P <0.05) was observed. The authors concluded that sirolimus therapy slowed down lung function decline and increase in cystic lesions. Most patients were able to tolerate sirolimus therapy.

Sirolimus decreases circulating lymphangioleiomyomatosis cells in patients with lymphangioleiomyomatosis.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3883264/

The authors group investigated the effect of sirolimus, a mTOR inhibitor, on circulating LAM cells. They utilized the FACS-based method to isolated LAM cells from blood and urine. They identified LAM cells with TSC2 LOH in 100% of blood specimens and 75% of urine samples from patients before therapy. However, over a mean duration of 2.2 ± 0.4 years of sirolimus therapy, detection rates of LAM cells were significantly decreased to 25% in blood (P = 0.001) and 8% in urine (P = 0.003). Following therapy, a greater loss of circulating LAM cells was seen in postmenopausal patients (P = .025). The authors concluded that sirolimus yielded a progressive loss of circulating LAM cells that depended on time of treatment and menopausal status.

Exonic mutations of TSC2/TSC1 are common but not seen in all sporadic pulmonary lymphangioleiomyomatosis.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3733437/

The authors revealed that not all LAM cells, in fact only a small fraction of them, carry TSC mutations. In this study, LAM cells were microdissected from paraffin-embedded specimens of 10 patients with sporadic LAM, then examined for exonic sequences of TSC1 and TSC2 genes by using a next-generation sequencer. Somatic mutations identified were nine different pathogenic TSC2 mutations in eight of these patients. However, allelic frequencies of the mutations ranged from 4 to 60% but, most often, less than a 20% frequency. Four of these eight patients'
samples showed TSC2 two-hit inactivation. Interestingly, two patients with sporadic LAM showed no TSC1/TSC2 mutation. The important considerations as to the pathogenesis of LAM raised here are; 1) TSC2 mutations may not be the primary driver of LAM development but occur in a subset of LAM cells after other unknown initiating events; 2) TSC2-mutant cells may recruit stromal cells to adopt a LAM cell phenotype; and 3) the existence of the two individuals without TSC1 or TSC2 mutations suggests that alternative genetic mechanisms may be operative in some cases of LAM.