Review Article

Lymphangioleiomyomatosis and mTOR inhibitors in real world—a narrative review

Sanghoon Park[1]^, Eun Joo Lee[2]^

[1]Nokhyang Medical, Siheung-si, Gyeonggi-do, Korea; [2]Division of Respiratory, Allergy, and Critical Care Medicine, Korea University College of Medicine, Korea University Medical Center, Seoul, Republic of Korea

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Correspondence to: Eun Joo Lee, MD, PhD. Division of Respiratory, Allergy, and Critical Care Medicine, Korea University College of Medicine, Korea University Medical Center, 73, Goryeodae-ro, Seongbuk-gu, Seoul 02841, Republic of Korea. Email: nanjung@korea.ac.kr.

Background and Objective: Lymphangioleiomyomatosis (LAM) is a rare disease developing mostly on lung and leading to various pulmonary and extra-pulmonary manifestations. Management of this intractable illness has been mostly symptomatic and supplementary until the advent and application of a novel drug, i.e., the mechanistic target of rapamycin (mTOR) inhibitor, and successful disease control using mTOR inhibitors is improving LAM patients. Although mTOR inhibitors are showing remarkable results there are still many rooms for further progress, and partly solved issues on problems seen in LAM still remain. We searched multiple reports and investigational studies regarding LAM, especially the therapeutic achievement won by mTOR inhibitors. This article summarized several characteristics of LAM including pathogenesis, clinical manifestation, laboratory findings, and management. We also attempted to review the latest knowledge and efficacy of mTOR inhibitors and some new drugs.

Methods: Online searching of literature was performed. The National Center for Biotechnology Information (NCBI), PubMed, Cochrane Library, Google Scholar, and EMBASE were searched.

Key Content and Findings: LAM is a genetic disease with a high predilection toward female subjects. Not only lung but also other organs are involved, hence extrapulmonary symptoms and signs are also noted. Representative objective finding is a progressive deterioration of lung function, sometimes leading to respiratory failure. Supportive and symptomatic care has been the mainstay of therapy with suboptimal result, until a novel drug, the mTOR inhibitor, was developed. Successful deterrence of disease progression was achieved on management with mTOR inhibitors. Several unsolved problems using mTOR inhibitors are a pending issue, such as duration of treatment.

Conclusions: LAM has been a rare, stubborn disease to ameliorate in health due to its complex pathogenesis and accompanied by other manifestations. Adopting various tools for relief has been usually suboptimal, but mTOR inhibitors proved to achieve significant improvement in various aspects. Further investigation is needed including refinement of currently available therapeutic applications, development of novel remedies, and so on.

Keywords: Lymphangioleiomyomatosis (LAM); management; mechanistic target of rapamycin inhibitor (mTOR inhibitor)

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^ ORCID: Sanghoon Park, 0000-0001-5900-8339; Eun Joo Lee, 0000-0001-7884-9045.

Introduction

Lymphangioleiomyomatosis (LAM) is a rare pulmonary disease, a slowly progressive, low-grade, metastasizing neoplasm mostly involving women of reproductive years (1-3). LAM is mainly characterized with metastasis of abnormal smooth muscle-like cells (i.e., LAM cells) to the lung, resulting in cystic formation replacing lung parenchyma, eventually leading to lung destruction and respiratory failure (4,5). LAM cell is the core entity of this obstinate disease but the origin of these cells is not well known, with several potential source sites such as the lung per se, angiomyolipoma, uterus, or lymphatic system. Therefore, it is commonly assumed that extra-pulmonary LAM cells might reach the lung via the lymphatic system or bloodstream. These cells intrude the lymphatic system and clog lymphatic flow, causing chylous pleural effusion and ascites (6). Not only pulmonary but other organs show manifestations in LAM, including kidney, lymphatic system, liver, digestive system, or even meningeal tissues.

High suspicion on diagnosis is required when a female subject presents with a recurrent spontaneous pneumothorax, or progressive dyspnea (7). Initial questioning may ensue appropriate laboratory, radiographic, and pathological evaluation for differential diagnosis and confirmation of LAM.

The aim and interest of this article is to update our knowledge of this peculiar disease, regarding from pathogenesis, clinical and laboratory manifestation and also to prognosis. We also attempted to summarize the latest trend and result of management, mainly focusing on pharmacological treatment. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-778/rc).

Methods

An online search of literature was conducted. The National Center for Biotechnology Information (NCBI), PubMed, Google Scholar, Cochrane Library and EMBASE were searched. All literature published in English between January 1990 to April 2023 were included. On searching, we combined various words; main searching keyword 'lymphangioleiomyomatosis' was combined with the following words such as 'pathogenesis', 'pathology', 'pharmacotherapy', 'treatment', 'prognosis', etc. The search strategy is summarized in *Table 1*.

Pathogenesis

LAM is a genetic disease, developing as a germline and/or somatic mutation, altogether resulting in a multiorgan systemic disease. LAM is commonly classified into two types, depending upon the presence (or absence) of underlying genetic disorder called tuberous sclerosis complex (TSC) (8). TSC, a multisystem genetic illness, is developed via germline or somatic mutation on two specific genes, TSC1 (encoding hamartin) and TSC2 (encoding tuberin) (9). LAM is one of various manifestations seen in TSC, and therefore when a LAM occurs to individuals subjected to TSC an appellation of "TSC-LAM" is used. On the other hand, a somatic mutation in TSC2 gene also occurs in a sporadic fashion in subjects not stricken with TSC, accordingly designated as "sporadic LAM".

The core pathogenesis of LAM is a genetic disruption of complicated signaling pathways in multiple directions ranging from angiogenesis, cell proliferation, and lymphangiogenesis to proteolysis, apoptosis, or metastasis, all resulting in excessive proliferation of LAM cells (10). Several bioactive molecules and chemokines/chemokine receptors are known as key constituents of this intractable disease, and thus are discerned as targets of diagnosis, treatment or follow-up marker after management. Of those, the mechanistic target of rapamycin (mTOR) is the essential component for disease control (11,12). Overactivity of mTOR causes excess cellular growth and proliferation, and primes patients to develop the benign tumors characteristic of LAM (13). Upregulated bioactive molecules such as angiogenic factor vascular endothelial growth factor (VEGF)-A, and lymphangiogenic factor VEGF-C and -D facilitate formation of blood vessels and lymphatic channels, respectively, contributing to access of LAM cells to the main blood stream and lymphatic circulation (10). Specifically, serum VEGF-D level is commonly utilized as an auxiliary tool on diagnosis (see below).

LAM is a disease that has the strongest female predominance among neoplasms arising from non-urogenital system (10). LAM is a nearly exclusive disease arising from female subjects, and therefore female hormones and menstrual cycles are linked to its clinical presentation. For instance, menopause ameliorates the decline rate of forced expiratory volume in 1 second (FEV_1) and progression to death or lung transplantation (14). Several investigations, however, showed contradictory consequences regarding of anti-hormonal therapy, making utilization of sex hormonal tendency a controversial and

Table 1 The search strategy summary

Items	Specification
Date of search	April 25, 2023 (final day)
Databases and other sources searched	The National Center for Biotechnology Information (NCBI), PubMed, Google Scholar, Cochrane Library and EMBASE
Search terms used	'Lymphangioleiomyomatosis', 'pathogenesis', 'pathology', 'pharmacotherapy', 'treatment', 'prognosis'
Timeframe	January 1990 to April 2023
Inclusion criteria	Study types: systemic review, meta-analysis, review, clinical trials, observational study; language restriction: English only; species: human and other animals; age: adult
Selection process	Corresponding author independently reviewed the titles and abstracts of all retrieved studies to exclude irrelevant studies. Full-text reviews of all included studies were independently performed by both investigators. Disagreements were resolved by discussion

less-than-expected means toward LAM management (14).

Clinical manifestations

Clinical manifestations are largely grouped into pulmonary and extrapulmonary symptoms and signs. LAM patients may have almost no symptoms in their early stages. Two representative respiratory manifestations are dyspnea and pneumothorax. From an important study using the National Heart Lung and Blood LAM Registry, enrolled 230 subjects from six participating clinical centers showed breathlessness as the most common symptom (73.0%) (15). Pneumothorax had developed in 55.5% of enlisted subjects. Other manifestations were wheezing (46.5%), cough (30.9%), hemoptysis (30.4%), sputum (27.0%), pleural effusion (20.9%), and so forth. Forty-four percent of enrolled subjects had a history of pleurodesis, by medical or surgical methods. Extrapulmonary manifestations were also seen, such as renal angiomyolipomas (37.8%, predominant in TSC-LAM) or chylous ascites (4.3%). Abdominal lymphadenopathy is sometimes seen. Retroperitoneal lymphangioleiomyoma may be discovered in one instance (16). Abdominal manifestations sometimes precede verification of pulmonary lesions, and these leads do delayed diagnosis (17,18). Meningiomas in LAM are known to be more prevalent than that in the general population (19). While the prevalence of meningioma in general population is around 1:20,000 LAM patients contract more frequently (i.e., around 2–3%). Meningioma contains progesterone receptor, and progesterone has a mitogenic effect in LAM patients. For this reason, aside for weak evidence of beneficial effect toward LAM, hormonal therapy is no longer recommended (20); therefore, searching for meningiomas in LAM patients using imaging tools are accordingly less performed.

As of dyspnea, many LAM patients were initially misdiagnosed as bronchial asthma or chronic obstructive pulmonary disease (COPD). Lack of the typical improvement-exacerbation pattern or poor response to usual asthma/COPD treatment belatedly draws clinicians' attention, leading to further work-up process as follows.

Diagnostic process

Female subjects in their thirties or forties with spontaneous pneumothorax (especially repeated) is the representative clinical picture of LAM (7). This unusual finding will draw attention by physicians, and diagnostic tools are subsequently adopted as follows.

Radiological study

After discerning several peculiar clinical manifestations such as repetitive pneumothorax or intractable airway disease, subjects suspicious of LAM will be led to chest radiography, with subsequent high resolution computed tomography (HRCT) that provides additional detailed data about the disease in relation to the X-ray study. Characteristic finding on HRCT is cysts with thin walls, surrounded by normal lung parenchyma (20,21). Pulmonary cyst formation is (rather) a normal aging process, appearing in subjects aged 40 years or older, and up to 12.9% at age over 80 years. Araki *et al.* (22) exemplified that the prevalence of lung cysts from a general population of Framingham Heart Study cohort was 7.6%, developing on peripheral regions

of the lower lobes (65.5%). In this study, cysts were largely solitary (64%), size was circa 10 mm with generally no notable size increment. Multiple, especially with its count of five or more, pulmonary cysts may need investigation for the possibility of cystic lung disease. In contrast, cysts discovered in LAM patients measure 2 to 30 mm in diameter, seen as lucent or low-attenuated areas, and scattered bilaterally on subjects' lungs. These cysts count from a few scattered cysts to near complete replacement of the lung parenchyma (3). Ground-glass opacity (GGO) is another finding, stemming from lymphatic fluid collection in alveoli, hemorrhage, lymphatic congestion, or hemosiderosis (23). GGOs are focally distributed, admixed with cysts or small centrilobular nodules.

Pulmonary function test

On spirometry and plethysmography, airflow obstruction pattern is the most common finding; in view of LAM as one of the interstitial lung diseases, this manifestation is a unique feature (10). On the other hand, restrictive or mixed patterns are also seen in LAM patients. Limitations to airflow and corresponding reduced flow rates (FEV_1) are also noted in LAM patients (24). Rate of FEV_1 decline is associated with baseline disease severity (14). The bronchodilator response may indicate disease activity. Several parameters are suggested showing a faster rate of FEV_1 decline (see below, Prognosis section).

Laboratory findings

Among several biomarkers, serum VEGF-D is a proven tool for diagnosis of LAM. The American Thoracic Society and Japanese Respiratory Society claimed application of serum VEGF-D as a useful test for a female with a compatible CT finding suspicious of LAM (20). The value of greater than 800 pg/mL is both sensitive and specific for the confirmation of LAM, not requiring any pathologic definitive diagnosis. One Japanese study verified its utility on diagnosis of LAM, corroborating the recommendations from the two academical societies (25). Of note, cutoff value of serum VEGF-D level at a specific 645 pg/mL showed a sensitivity and specificity of 0.83 and 0.97, respectively, whereas those of the recommended cutoff level (i.e., 800 pg/mL) were 0.72 and 1.00, respectively, expressing a slightly less sensitive result. Heightened serum VEGF-D level is considered also as a possible target of management (26). However, serum VEGF-D level measurement is not easily available in some countries, limiting the usefulness of this marker in the clinical practice.

Pathology

For tissue procurement, video-assisted thoracoscopic surgery (VATS)-guided surgical lung biopsy was previously the gold standard (20), and less invasive methods including transbronchial lung biopsy (TBLB) or transbronchial lung cryobiopsy (TBLC) are being adopted recently (10). A study of 75 subjects including some LAM patients proved TBLC as an effective and safe diagnostic modality (27). Several case reports of TBLC for LAM were also noted (28,29). Nonetheless, VATS-guided biopsy is applied when less invasive diagnostic tools are insufficient on a confirmatory process due to nearly 100% diagnostic yield (10).

Management up-to-date

Management of LAM is largely categorized into two aspects: symptomatic treatment of accompanied complications and fundamental, pathogenesis-based correction using several novel remedies. Pharmacological mainstay of LAM management is mTOR inhibitors. mTOR inhibitors (sirolimus, everolimus) suppress mTOR signaling in LAM patients, hence inducing interruption of lung function degradation, decrement of lymphangioleiomyoma burden, and improvement of pulmonary (i.e., chylous effusion, chyloptysis, etc.) and extra-pulmonary (chylous ascites, bleeding from renal angiomyolipoma, etc.) complications (30,31). Functional performance and quality of life are also improved. The main mechanism of mTOR inhibitors is not an ablative concept, and therefore the duration of administration is accordingly indefinite. In other words, discontinuation of mTOR inhibitors will lead to loss of therapeutic effects such as decreased lung function, recollection of chylous pleural effusion or ascites, and other problems. Adverse effects of mTOR inhibitors were predictable, considering the immunosuppressant nature of the therapeutic mechanism.

A number of studies have been reported regarding the effect and usefulness of mTOR inhibitors for LAM treatment. Due to rarity of this specific illness, a properly designed clinical investigation is scarce and consequently observational reports prevail lately. Nevertheless, most of the research reports support the worth of mTOR inhibitors, and The American Thoracic Society and Japanese Respiratory Society clinical practice guidelines recommend

using sirolimus as first-line treatment for patients with LAM who meet at least one of the following criteria: percentage of predicted FEV_1 of 70% or less, chylous complications, rapidly declining lung function (FEV_1 decline ≥90 mL per year), or other measures suggesting substantial disease burden such as abnormal diffusion capacity, air trapping, hyperinflation, or the need for supplemental oxygen (32).

Sirolimus was the beginning of immunology-based therapy of LAM. An open label, phase 1–2 trial was first performed on subjects of TSC-LAM also having angiomyolipomas larger than 1 cm. After verifying the efficacy on preclinical study, sirolimus administration resulted in size decrement of angiomyolipomas (but re-enlarged after discontinuation of therapy), and retainment of pulmonary function (33). Although there was no control group and the sample size was small in this investigation, this was the first clinical report to show validity of sirolimus.

After the previous research, a multinational randomized controlled trial (RCT) was reported (12). Dubbed as MILES Trial, its primary outcome was rate of change of lung function between control and case groups. Randomly assigned 89 subjects were administered sirolimus or placebo for 1 year, and thereafter discontinued and observed for 1 year. Sirolimus showed beneficial effects toward LAM in various aspects such as FEV_1 stabilization, forced vital capacity (FVC) improvement, quality of life improvement, or lowering of serum VEGF-D levels. Although the improved FEV_1 declined back to pretreatment baseline in both groups, (notably) change of FVC did not deteriorate in the case subjects. Serious adverse events showed similar rates between groups with an increased frequency of adverse event in the treatment group. This investigation was the first randomized controlled study proving the efficacy of sirolimus on lung function of LAM.

In a single center observational study collecting data from 98 female Chinese subjects stricken with S-LAM and who were administered sirolimus and tracked for median 2.5 years, sirolimus improved examinees in many aspects including physical performance [physical fitness test (PFT), six-minute walking test (6MWT), etc.], objective measurements (arterial blood gas analysis, serum VEGF-D levels, etc.), and other pulmonary (chylous effusions and chylothorax) and extra-pulmonary manifestation (renal angiomyolipomas) (34). Subjects with TSC-LAM were uniquely excluded from the study, and some difference of clinical manifestation between TSC-LAM and S-LAM (i.e., predominance of lymphatic complication more common on S-LAM) may be considered on interpretation.

Optimizing the safe and appropriate therapeutic dose of sirolimus for LAM was studied by a single center of Korea (35). Lower dosage (<5 ng/mL) of sirolimus proved inferior efficacy compared with regular dose (5–15 ng/mL) in this investigation. However, considering the subtle heterogeneity of two study groups and slight predominance of renal complication in the LAM-stricken subjects, attention is required on interpreting this result.

One radiological observational study showed sirolimus attenuated the increment of lung cysts volume accompanied in LAM, and even decreased volume of lung cysts (36). Authors claimed that cysts in lung improved in both quantitative (computer software-assisted method) and qualitative (thoracic radiologists) evaluation. This investigation exemplified the possibility of CT as a useful marker of disease survey, although radiational exposure will be an obstacle for practical utilization.

A nationwide cohort study from the United Kingdom enlisting LAM patients (n=47) managed with sirolimus investigated the effect of lung function improvement (5). In this study, although most of the subjects experienced reduction of lung function loss some showed poorer response to treatment; authors postulated this variability of post-treatment FEV_1 change as a "resistance to sirolimus" stemming from other signaling pathways other than mTOR mechanism such as specific phenotypes or drug sensitivity. Management of LAM, therefore, is recommended by authors to start early to preserve lung function, for poor response was associated with longer disease duration and lower baseline (pre-treatment) lung function.

Before sirolimus being adopted in clinical practice, another mTOR inhibitor, everolimus, was evaluated for validation. Everolimus is a second-generation, a 40-*O*-(2-hydroxyethyl) derivative of sirolimus. Different functional groups added at this C40 position enables mTOR inhibitor analogs vary in terms of important clinical implications (37). Hence, there are stark difference between these two substances in terms of pharmacodynamic, pharmacokinetic and toxicologic perspective (38). Everolimus is known to be superior to the kindred drug as having a higher bioavailability, a shorter terminal half-life (and accordingly faster elimination after discontinuation), different blood metabolite patterns, an ability to stimulate brain mitochondrial oxidation, and so on.

A multicenter, randomized controlled, phase 3 trial was conducted to patients having angiomyolipomas, with primary endpoint of targeted angiomyolipoma mass volume reduction defined as a ≥50% reduction in the volume of target lesion (39). In this study (named as EXIST-2 study),

everolimus effectively reduced the mass with a response rate of 42%, compared with 0% response for placebo group. This study was further reported after a long-term use as a 4-year update, with subjects in placebo group were crossed over to everolimus 10 mg/day (40). Open-label extension phase switching enabled 58% of subjects to achieve volume reduction response.

A multicenter open-label study designed examining the usefulness of everolimus on LAM patients in terms of lung function was reported (41). From this phase 2 trial, authors reported that everolimus had a fair safety profile, improved subjects' lung function and reduced serum VEGF-D levels.

Everolimus was also evaluated regarding renal angiomyolipoma in an (another) small observational study. Researchers reported that renal angiomyolipoma lessened on 1-year duration of everolimus administration, and benefits were reversed on drug withdrawal (42). Lung function and skin lesions were also improved, albeit reversed after discontinuation of everolimus.

Investigations of mTOR inhibitors on LAM are summarized on *Tables 2,3*.

Table 4 shows the latest clinical trials regarding LAM treatment registered on the NIH ClnicalTrials.gov website.

Prognosis

Before the advent of mTOR inhibitors, LAM patients experienced progressive deterioration of lung function eventually leading to death or lung transplantation. Several aspects and subjects' characteristics were mentioned as prognostic markers.

FEV_1 decline is the representative sign of progression, showing variable rate of decline ranging from 47 to 134 mL per year (10). FEV_1 decline is linked to several prognostic markers. From the NHLBI LAM Registry (14), FEV_1 decline was faster on subjects with a higher initial FEV_1, higher FVC, a higher CT score, and a positive bronchodilator response. Of note, although some former studies proved the association between the baseline PFT result and its decline rate (44,45), the LAM Registry analyzed their cohort by dividing into four subgroups according to initial FEV_1 (i.e., >70%, 51–70%, 36–50%, and ≤35% of predicted FEV_1 values) and verified that FEV_1 decline rate was largely similar irrelevant to the baseline FEV_1. Investigators of the LAM Registry concluded that the decline rate of FEV_1 is grossly independent of baseline FEV_1, stressing that subjects with fair baseline PFT shall not be overlooked as a case of indolent prognosis. We believe this assertion (e.g., irrelevance of FEV_1 decline and baseline FEV_1) require further validation and research.

Predominant cyst distribution on subjects' LAM-stricken lung is expressed as so-called "higher CT score'. This CT score was calculated by evaluating disease extent by radiologists on upper/middle/lower lung zone of both lungs on CT, with a total sum of 18 points; higher CT score indicates a severe disease. Subjects responding to bronchodilator were predicted to have a worse prognosis beforehand (46), and authors of the LAM Registry reiterated that a positive bronchodilator group showed a lower baseline FEV_1. Several demographic characteristics were also related to the prognosis of LAM. An older age was linked with a slower FEV_1 decline. Menopausal status was another factor, and premenopausal state showed a faster FEV_1 decline rate compared with postmenopausal subjects.

Serum VEGF-D level is utilized as a diagnostic marker, severity indicator, and also as a prognostication tool. While some study described irrelevance of serum VEGF-D and decline rate of FEV_1 (14), correlation and usefulness of the VEGF-D level as a prognostic gauge is predominantly supported by other investigatory reports (47,48).

Subjects with TSC-LAM are estimated to have a more indolent course than those with S-LAM (49). However, it has been noted that there is a probability of ascertainment bias on this knowledge.

Conclusions

LAM has long been a rarely discovered ailment with various symptoms and complications harassing patients lifelong. From this review, LAM is regarded as an intractable, long-period-continuing, but fairly controllable illness. Thanks to the development of mTOR inhibitors based on studies of molecular biology, LAM is shifting its position from an intractable, poorly controlled disease to a manageable illness.

However, there are still unsolved and misunderstood problems regarding the management of LAM. For example, lifelong period of management on using mTOR inhibitors is inevitable so far, and discontinuation of treatment naturally leads to aggravation of LAM. An age too young on starting mTOR inhibitors can induce a lengthy treatment, maybe causing decades of period. Accordingly, considering many aspects such as cost of treatment, obedience of patients on management, and side effects all lead to concern of timing of initiation for treatment.

Various side effects during mTOR inhibitor administration are of concern to clinicians, and optimal titration of dosage

Table 2 Sirolimus studies

Author [year]	Study type (country)	Inclusion (number)	Treatment	Primary outcome	Secondary outcomes	Results	Adverse effects
Bissler *et al.*, [2008] (33)	Open label, non-randomization, single center, phase 1–2 (USA)	Angiomyolipoma (>1 cm) in TSC only (n=7), TSC-LAM (n=12), LAM (n=6)	Treatment 1 year + observation 1 year	Angiomyolipoma volume at 1 year	Angiomyolipoma volume at 2 years; lung function test; 6MWT; percent of the cystic volume at 1 & 2 years	Angiomyolipomas regressed during therapy; angiomyolipomas increased in volume after sirolimus therapy was stopped; some patients showed improvement in lung function with treatment	Aphthous ulcer, diarrhea, upper respiratory infection, leukopenia, thrombocytopenia, hypertriglyceridemia, delayed wound healing
McCormack *et al.*, [2011] (12) (MILES trial)	RCT (1:1), multicenter, phase 1–2, (USA, Japan, Canada)	Sporadic/TSC-LAM, FEV_1 ≤70% (N=89)	Treatment 1 year + observation 1 year	Rate of change in FEV_1	FVC change at 12 months; lung volume; 6MWT; DL_{CO}; serum VEGF-D; QoL	Sirolimus stabilized lung function; sirolimus reduced serum VEGF-D; sirolimus reduced symptoms; sirolimus improved QoL	Mucositis, diarrhea, nausea, hypercholesterolemia, acneiform rash, swelling in the lower extremities
Taveira-DaSilva *et al.*, [2011] (30)	Observational study, single center, off-label (USA)	Rapid progressing LAM or chylous effusion (n=19)	Off-label therapy (mean duration: 2.6 years)	Changes in lung function, chylous effusion, lymphangioleiomyoma		Sirolimus improved or stabilized lung function; sirolimus reduced chylous effusion/ lymphangioleiomyoma	Mouth ulcer, hyperlipidemia, acne, worsening hypertension, diarrhea, neutropenia
Takada *et al.*, [2016] (43)	Open label, single arm (Japan)	LAM treated with sirolimus (n=63)	2-year study period	Frequent of AEs and SAEs	FEV_1 & FVC response, QoL	Most frequent events were mucositis, pharyngitis, upper respiratory infection, acneiform rash, headache; SAEs included sirolimus-induced pneumonitis, bronchitis, acute respiratory failure, small bowel obstruction and herpes zoster; no change in QoL; lung function was stable over the course of 2 years on sirolimus	
Yoon *et al.*, [2018] (35)	Retrospective, single center (South Korea)	LAM treated with sirolimus (n=39)	Conventional dose *vs.* low dose (sirolimus level <5 ng/mL)	Efficacy (lung function), safety		Low dose sirolimus may stabilize lung function decline; efficacy of low dose sirolimus was inferior to that of conventional dose	There were no significant differences in adverse events between the groups
Bee *et al.*, [2018] (5)	Prospective national observational cohort (UK)	Sirolimus treated for LAM subjects of progressive lung disease (n=47)	More than 1 year	Lung function response, side effect		Sirolimus reduced lung function loss	Aphthous ulcer, nausea, diarrhea, acne, edema, menstrual irregularities

TSC, tuberous sclerosis complex; LAM, lymphangioleiomyomatosis; 6MWT, six-minute walking test; RCT, randomized controlled trial; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; VEGF-D, vascular endothelial growth factor-D; QoL, quality of life; AE, adverse effect; SAE, serious adverse effect.

Table 3 Everolimus studies

Author [year]	Study type (country)	Inclusion (number)	Treatment	Primary outcome	Secondary outcomes	Results	Adverse effects
Bissler *et al.*, [2013] (39) (EXIST-2 trial)	RCT (2:1), multicenter, phase 3 (USA, UK, Poland, the Netherlands, Russia, Japan, Germany, France, Spain, Canada, Italy)	Angiomyolipoma (>3 cm) in TSC/LAM (n=118)	Treatment until angiomyolipoma progression, occurrence of unacceptable toxicity	Proportion of patients with a confirmed angiolipoma response	Time to angiomyolipoma progression; skin lesion response rate; time to angiomyolipoma response; duration of angiolipoma, skin response; pharmacokinetics of everolimus; lung function; plasma angiogenetic molecules; safety	Angiomyolipomas response rate was 42%; higher skin lesion response was seen in everolimus group; median time to angiomyolipoma response was 2.9 months; everolimus was superior in time to angiomyolipoma progression	Stomatitis, nasopharyngitis, acne, headache, cough, hypercholesterolemia
Goldberg *et al.*, [2015] (41)	Multicenter, open-label, nonrandomization, phase 2 (USA, France, Italy)	LAM (n=24)	26 weeks (optimal extension period up to 62 weeks)	Safety, pharmacokinetics, serum VEGF-D	Lung function, 6MWT	Medication compliance was good (only 2 patients did not have 100% compliance); everolimus stabilized FVC; everolimus improved FEV_1 & 6MWT; everolimus reduced serum VEGF-D	Mouth ulceration, headache, nausea, stomatitis, fatigue, peripheral edema, pneumonia, cardiac failure, *Pneumocystis jirovecii* infection
Bissler *et al.*, [2017] (40) (extended study from EXIST-2 trial)	Open-label everolimus (extension phase)	Renal angiomyolipoma with TSC/LAM (n=112)	Median treatment time was 46.9 months	Angiomyolipoma response rate	Safety, response duration, time to angiomyolipoma response and progression	Fifty-eight percents of patients achieved angiomyolipoma response; almost experienced reduction in renal angiomyolipoma; 14% patients experienced angiomyolipoma progression at some point	Stomatitis, hypercholesterolemia, acne, aphthous stomatitis, nasopharyngitis
Cai *et al.*, [2018] (42)	Open-label everolimus, nonrandomization	Renal angiomyolipoma >3 cm in TSC/LAM (n=18)	Treatment 1 year + observation 1 year	Renal volume reduction of 50% or more without a new renal lesion ≥1 cm and no renal bleeding	Safety, lung function, skin lesions response rate	Everolimus reduced renal angiomyolipoma volume; everolimus improved lung function and skin lesions	Oral mucositis, irregular menstruation, abdominal pain, hypertriglyceridemia, headache

RCT, randomized controlled trial; TSC, tuberous sclerosis complex; LAM, lymphangioleiomyomatosis; VEGF-D, vascular endothelial growth factor-D; 6MWT, six-minute walking test; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second.

Table 4 Recently performed studies for management of lymphangioleiomyomatosis

Study title	Status	Conditions	Interventions	Study type	Phase	Number enrolled	NCT number	Title acronym	Study start
Effect of loratadine in lymphangioleiomyomatosis	Recruiting	Lymphangioleiomyomatosis	Drug: loratadine; drug: placebo 10 mg/day added to rapamycin for 12 months	Interventional	Phase 2	62	NCT05190627	LORALAM	November 1, 2021
Resveratrol and sirolimus in lymphangioleiomyomatosis trial	Completed/has results	Lymphangioleiomyomatosis	Drug: sirolimus; drug: resveratrol	Interventional	Phase 2	25	NCT03253913	RESULT	March 31, 2018
Multicenter interventional lymphangioleiomyomatosis (LAM) early disease trial	Recruiting	LAM; lymphangioleiomyomatosis	Drug: sirolimus	Interventional	Phase 3	60	NCT03150914	MILED	January 1, 2018
LAM pilot study with imatinib mesylate	Completed/has results	Lymphangioleiomyomatosis	Drug: imatinib mesylate 400 mg capsule; drug: placebo-capsule	Interventional	Phase 1/ phase 2	18	NCT03131999	LAMP-1	January 23, 2018
A study of nintedanib for lymphangioleiomyomatosis (LAM)	Completed	Lymphangioleiomyomatosis	Drug: nintedanib	Interventional	Phase 2	30	NCT03062943	LAM	December 6, 2016
Safety and efficacy of saracatinib in subjects with lymphangioleiomyomatosis	Terminated	Pulmonary lymphangioleiomyomatosis	Drug: saracatinib	Interventional	Phase 2	28	NCT02737202	SLAM-2	April 2016
COLA: a pilot clinical trial of COX-2 inhibition in LAM and TSC	Completed/has results	Lymphangioleiomyomatosis (LAM)	Drug: celecoxib	Interventional	Phase 2	12	NCT02484664	COLA	June 15, 2016
Safety and durability of sirolimus for treatment of LAM	Recruiting	Lymphangioleiomyomatosis	Drug: sirolimus; drug: everolimus	Observational		600	NCT02432560	MIDAS	March 2015
The tolerability of saracatinib in subjects with lymphangioleiomyomatosis (LAM) (SLAM-1)	Completed	Pulmonary lymphangioleiomyomatosis	Drug: saracatinib	Interventional	Phase 1	9	NCT02116712		August 2014
Safety of Simvastatin in LAM and TSC	Completed/has results	Lymphangioleiomyomatosis tuberous sclerosis complex	Drug: simvastatin; drug: sirolimus oral product; drug: everolimus oral product	Interventional	Phase 1/ phase 2	10	NCT02061397	SOS	March 2014

Table 4 (*continued*)

Table 4 (*continued*)

Study title	Status	Conditions	Interventions	Study type	Phase	Number enrolled	NCT number	Title acronym	Study start
Nebulized or inhaled albuterol for lymphangioleiomyomatosis	Recruiting	Lymphangioleiomyomatosis	Drug: albuterol inhaler; drug: albuterol nebulizer; procedure: PFT	Interventional	Phase 1/ phase 2	100	NCT01799538		June 10, 2013
Safety study of sirolimus and hydroxychloroquine in women with lymphangioleiomyomatosis	Completed/has results	Lymphangioleiomyomatosis	Drug: "sirolimus" and "hydroxychloroquine" 200 mg; drug: "sirolimus" and "hydroxychloroquine" 400 mg	Interventional	Phase 1	14	NCT01687179	SAIL	September 2012
Trial of aromatase inhibition in lymphangioleiomyomatosis	Completed	Lymphangioleiomyomatosis	Drug: letrozole; drug: placebo	Interventional	Phase 2	17	NCT01353209	TRAIL	May 2011
Doxycycline in lymphangioleiomyomatosis (LAM)	Completed	Lymphangioleiomyomatosis/ tuberous sclerosis	Drug: doxycycline; drug: placebo	Interventional	Phase 4	24	NCT00989742		July 2009

NCT, National Clinical Trial; LAM, lymphangioleiomyomatosis; PFT, physical fitness test.

is still an ongoing problem. All these problems may lead to studying an alternative strategy based on mTOR inhibitors with decreased dosage. Some useful candidate combination therapy regimens using mTOR inhibitors with other medication are therefore on discussion among researchers, in order to lessen unwanted side effects by reducing dosage of mTOR inhibitors, and additionally obtaining auxiliary or additive therapeutic effects. All these matters are essential for flawless management strategy of LAM patients.

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Footnote

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