

Review Article

Advances in understanding of lymphangioleiomyomatosis: current and emerging treatment options

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Abstract: We reviewed the history and the current status of Lymphangioleiomyomatosis (LAM) in Western countries and China. LAM is a kind of slow progressive lung disease because the smooth muscle cell abnormal proliferation invades the lung parenchyma and pulmonary lymphatic vessels. The main primary pathobiology is the multiple nodules and cystic lesion of the lung because of abnormal proliferation of the immature smooth muscle cells and perivascular epithelioid cells. Lung transplantation is the most effective treatment at present. However, LAM may recur with the same metastatic mechanism in transplanted lungs. Benefit from the deep research based on molecular biology and the development of the targeted therapy in medical treatment, the mammalian target of rapamycin (mTOR) inhibitor is a better choice for LAM patients rather than doxycycline or hormonal therapy. Although some studies have shown that mTOR inhibitors have favorable outcomes, the long-term efficacy needs to be further evaluated in larger clinical trials. This article summarizes the clinical characteristics for LAM, and current and emerging treatment options are the emphasis.

Keywords: Lymphangioleiomyomatosis (LAM), mTOR inhibitor, sirolimus, rapamycin

Introduction

Lymphangioleiomyomatosis (LAM) is a rare lung disease characterized by extensive cystic lesions that primarily affects women. The basis of LAM is the damage of the lung tissue and the cystic reconstruction, which is caused by abnormal proliferation of the pulmonary lymphatic vessel smooth muscle cells. LAM occurs sporadically or associates with the tuberous sclerosis complex (TSC) [1, 2]. The most common clinical manifestation, dyspnea, occurs in most of LAM patients within 10 years of symptom onset, and it gets worse gradually with the development of the disease [3]. Lung function decline can surpass typical age-related decline at rates by two to four times or more [4]. Some patients develop the recurrent pneumothorax, chylous fluid accumulations and occasional haemoptysis [1]. However, therapeutic medical

interventions for LAM were limited. Lung transplantation is the definitive treatment option for patients who get an advanced stage of LAM [5]. Recently, some studies show that mammalian target of rapamycin inhibitors such as sirolimus can stabilize lung function and reduce chylous effusions in LAM patients [6]. In addition, some studies indicated that the hormonal therapy and doxycycline therapy has less benefit for the patients. National Heart, Lung, and Blood Institute (NHLBI) established a national LAM registry in 1997 [7], and European Respiratory Society has published the first guideline about LAM in 2010 [8]. Although confirmed cases of the LAM reported increase than before in recent years, missed diagnosis rate is higher and efficacy rates is lower due to lack of understanding of the pathogenesis and therapy of LAM. This paper summarizes the current research status of PLAM in order to improve the

understanding of LAM, especially current and emerging treatment options.

Advances in understanding of pathophysiology in LAM

Understanding the pathophysiology in LAM has been pivotal to progress in LAM therapy. LAM occurs almost in adult women, affecting approximately 5 per 100,000 population [9]. It has been reported less in adult men and children. The primary pathobiology includes the abnormal proliferation of perivascular epithelioid cells and smooth muscle-like cells [10]. Matrix metalloproteinases (MMPs) include more than 25 extracellular matrix-degrading, zinc-dependent enzymes. Over-expression of MMP-2 and MMP-9 in the LAM cells has been found by immunohistochemical studies [11]. Although MMPs over-expression is related to various chronic pulmonary diseases, MMP-2 and MMP-9 predominantly express in lung tissue adjacent to cystic areas in patients with LAM [12]. It means that MMPs is likely to contribute to cyst formation in LAM. LAM cells also express common smooth muscle antigens (S100) and melanoma-related antigens (HMB-45, gp-100, MART-1) [8].

Due to the fact that the LAM occurs almost in women, hormonal factors were believed to play an important role in the pathogenesis of it [13]. Furthermore, being in the menstrual cycle, using acyeterion or treating with exogenous estrogen will make the disease worse [14]. Some patients would get worse or suffer more complications during pregnancy or childbirth [15]. In addition, LAM cells express both estrogens and progesterone receptors, especially in postmenopausal women with LAM [16]. But some studies showed that there is no benefit for LAM patients who received hormonal therapy [17].

In 1937, it was reported that LAM patient had not TSC. Over time, the LAM includes TSC-associated (TSC-LAM) and sporadic form (s-LAM). LAM occurs in women who may have germline mutations in either TSC1 or TSC2. Moreover, TSC2 mutations are more prevalent in the TSC-LAM population and tend to cause more severe clinical manifestations [18]. Some studies show that women with s-LAM do not have germline mutations in TSC2 [19]. Nevertheless, LAM cells from some women show the loss of het-

erozygosity of chromosome 16p13, suggestive of inactivation of the wild-type TSC2 allele. Consistently, FISH analyses of women with LAM have illuminated that the majority patients have loss of heterozygosity in the TSC2 region in chromosome 16p13 [19]. Moreover, a genetic analysis of angiomyolipomas for activating and inactivating mutations revealed only mutations in TSC2 and not TSC1 mutations recently [20].

LAM cells also express the lymphangiogenic proteins, such as VEGF-C and VEGF-D. Vascular endothelial growth factor D (VEGF-D) is a kind of lymphatic growth factor, which can induce the formation of lymphatic vessels and promote the spread of tumor cells to lymph nodes. Serum VEGF-D levels were normal in women with other cystic lung diseases, including lymphoid interstitial pneumonia and pulmonary Langerhans cell histiocytosis, but were elevated in LAM. According to the disease manifestations, serum VEGF-D levels appear various. VEGF-D is a useful biomarker associated with disease severity and response to treatment. Maybe, Serum VEGF-D can serve as a potential prognostic and predictive biomarker [21]. It may also help stratify patients in order to reduce the number of patients required for clinical trials.

The mTOR is a kind of serine/threonine protein kinase downstream of PI3K/PKB signaling pathway, which is associated with the development of cancer and is a central regulator of nutrients, energy and growth factors signals. It plays an important role in the cell growth and apoptosis that takes part in the biological process of gene transcription, protein translation, and synthetic ribosome [13]. The mTOR consists of mTORC1 and mTORC2, which have different activations and function. Generally, the mTORC1 mainly control the suppression of catabolic processes and the activation of anabolic processes, such as protein synthesis, lipid synthesis, ribosome synthesis and mitochondrial biogenesis.

LAM is caused by inactivating mutations in TSC genes; and the defective TSC genes activate the mTOR pathway. Moreover, the activated mTOR perturb multiple cellular processes. Recently, with so much focus on the mTOR pathway, mTOR inhibitors, such as sirolimus and everolimus, have demonstrated considerable

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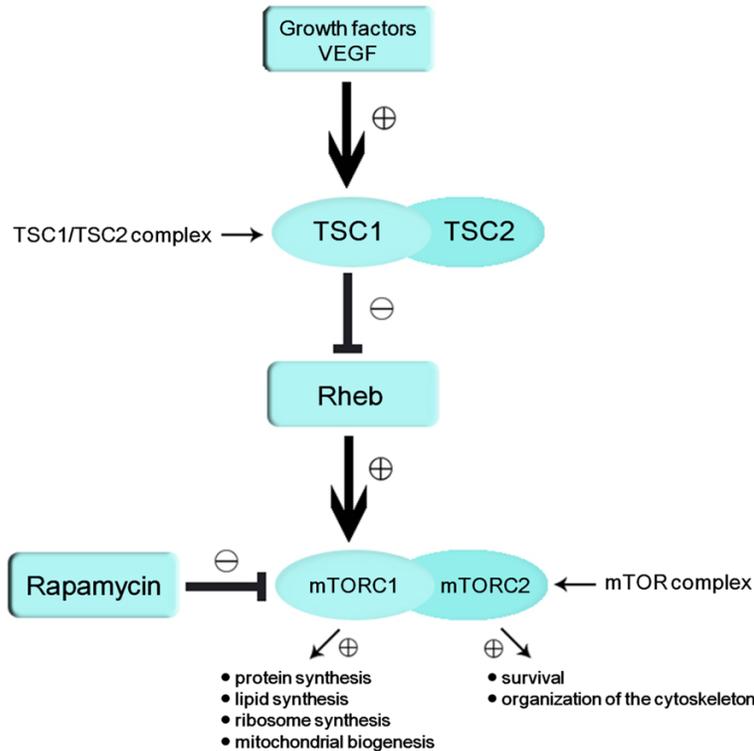


Figure 1. A simplified diagram of the mTOR pathway. The mTOR complex responds to multiple extracellular irritants, such as growth factors, insulin, and VEGF, etc. It mainly requires a PI3K/Akt/mTOR pathway to function. Normally, TSC1/TSC2 complex is an inhibitor of Rheb, which is the indispensable stimulating protein to activate mTOR complex. The TSC1/TSC2 complex inhibits the function of mTOR in normal condition. Regulation of phosphorylation of TSC2 inhibits the formation of TSC1/TSC2 complex. So, the mTOR will be abnormally activated without the inhibition of Rheb. That is that owing to the inactivation of TSC genes, it is inefficient to inhibit Rheb; and mTOR complex expresses abnormally. Rapamycin can inhibit mTORC1 to avoid excessive proliferation of LAM cell.

prospects for treatment of neuroendocrine tumor, renal cancer, and breast cancer in a series of clinical studies. In the latest guideline [17], for LAM patient with abnormal/declining lung function, it recommends sirolimus as the treatment rather than observation. The evidence for recommended treatment is strong. The mTOR therapy may improve functional performance, stabilize lung function, and improve overall quality of life.

The following is a simple explanation about the mTOR pathway (**Figure 1**). The mTOR complex responds to multiple extracellular irritants, such as growth factors, insulin, and VEGF, etc. It mainly requires a PI3K/Akt/mTOR pathway to function. Normally, TSC1/TSC2 complex is an inhibitor of Rheb (Ras homolog enriched in brain, a kind of GTPase with small molecular weight) which is the indispensable stimulating

protein to activate mTOR complex. Therefore, TSC1/TSC2 complex inhibits the function of mTOR in normal condition. Regulation of phosphorylation of TSC2 inhibits the formation of TSC1/TSC2 complex. So, the mTOR will be abnormally activated without the inhibition of Rheb. It is now believed that the abnormal proliferative activity of LAM cells is contributed by the loss of function of the tuberous sclerosis complex (TSC1/TSC2) which is an essential tumor suppressor [22]. Owing to the inactivation of TSC genes, it is inefficient to inhibit Rheb; and mTOR complex expresses abnormally.

Moreover, the abnormal proliferation of LAM cell may cause the formation of lung cysts; and its mechanism is poorly understood. The actual destruction of the lung parenchyma may contribute to cystic lesions. Some studies show that LAM cell proliferation obstructs the airways and leads to the distention of alveolar units [10, 23].

Clinical features

The typical presentation of patients with LAM is progressive airflow obstruction, which leads to respiratory failure and pulmonary heart disease. Patients with LAM usually develop pneumothorax and cough. Chylous pleural effusions and occasional haemoptysis may occur as well. Immature smooth muscle abnormal proliferation can narrow or jam the bronchiole, lymphatic and small blood vessel in lung, bronchus, which generally causes cystic ectasis diffusely. Pneumothorax occurs in two-thirds of women with LAM due to the cystic lesion rupture. Furthermore, these are recurrent in more than two-thirds of pneumothorax patients [1]. If lymphatic backflow of lymphatic or thoracic duct obstructs, chylous pleural effusions would appear. The LAM patients develop haemoptysis when severe outstretched small pulmonary veins broke because of the blood circulation disorder.

Lung function tests in patients with LAM show various abnormalities with airflow obstruction. Sometimes, restrictive dysfunction of pulmonary ventilation may be seen, but usually combine with airflow obstruction. Diffusing capacity of the lungs can reduce remarkably. Mixed ventilatory disorders are often the result of pleural effusions [24]. Arterial blood gas analysis shows hypoxemia but not obvious retention of carbon dioxide in patients with LAM [7]. Bronchial provocation test and (or) dilation test were positive in a few patients. Diffusing capacity of the lung for carbon monoxide (D_{LCO}) is regarded as a sensitive indicator of LAM progression. In addition, it reflects the integrity of the pulmonary capillary bed. FEV_1 (forced expiratory volume in 1 second) and D_{LCO} is correlated with the severity of pathological changes in patients with LAM, and change over time as the disease progresses [16, 25].

Diagnosis

Because LAM is often missed diagnosis or misdiagnosis, it is the key to get the correct diagnosis by improving the understanding of the characteristics of the disease and maintaining the vigilance of the suspicious patients. Once the female patient presented with unexplained dyspnea, combined with recurrent pneumothorax (especially bilateral pneumothorax or chylothorax), should be performed to exclude LAM by high-resolution computed tomography (HRCT). Clinical diagnosis is supported by model clinical manifestation and characteristic cystic lesions from HRCT. The diagnosis can be established without pathological conditions if the patients also have tuberous sclerosis, renal angiomyolipoma, or chylothorax. Pathological examination is helpful for the diagnosis, including the pathological changes of the lung or extrapulmonary. However, the diagnosis of LAM does not always require pathology.

The early performance of LAM is dyspnoea, easily leading to misdiagnosis. Women should be suspected as LAM if they got dyspnoea or asthma associated with pneumothorax, haemoptysis or abnormal chest radiograph. Lung biopsy has been the gold criteria for the diagnosis of LAM. Lung biopsy can define the hormone receptor status of LAM cells. It can also make sure whether cystic changes or smooth muscle proliferation predominates. The typical pathological changes of LAM include the ab-

normal proliferation of perivascular epithelioid cells and immature smooth muscle. It found that the monoclonal antibody HMB45 stain LAM cells in the lung with the improvement of the sensitivity and specificity of histological analysis. Video-assisted thoracoscopic or transbronchial lung biopsy combining HMB45 staining can be adequate to make a diagnosis of LAM. The finding of chylous effusion or renal angiomyolipomas can strengthen the diagnosis. Although serum VEGF-D varies on the basis of the disease manifestations, it has been recommended as a diagnostic test of LAM [17].

Characteristic features of pulmonary LAM on HRCT

A standard posteroanterior and lateral chest radiograph has limited value in LAM patients. The plain radiograph may be normal initially. Reticular shadowing and cystic changes, which may also be seen in Langerhans' cell histiocytosis and sarcoidosis, develop as the disease progresses. A high-resolution computed tomography scan is commonly used to diagnose LAM. The characteristic appearances are multiple thin-walled round well-defined air-filled cysts distributed throughout the lung fields (**Figure 2**). Lung cysts are the hallmark lesion and present in all patients with LAM. They vary typically ranging from 2-20 mm in diameter [26].

However, the usefulness of HRCT in differentiating LAM from other diffuse cystic lung diseases is undefined. However, the accuracy of diagnosing LAM diffuse cystic lung diseases based on HRCT was higher than non-LAM [27]. According to the European Respiratory Society guidelines, without a tissue biopsy, it is sufficient to diagnose LAM confidently with the characteristic HRCT features along accompanying by any of the following clinical manifestations: tuberous sclerosis complex, cystic lymphangioleiomyoma, renal angiomyolipoma or chylous pleural effusions in the chest and (or) abdomen [8].

FEV_1 and T_{LCO} (transfer factor of the lung for carbon monoxide) declines in most patients with LAM and T_{LCO} may be more abnormal than FEV_1 in the early stage of LAM. Nevertheless, the rate of decline varies among patients and it is difficult to predict the clinical course in individuals. According to Japanese National LAM Registry, the reduction in FEV_1 is approximately 46.7 ml per year [28]. Cardiopulmonary exer-

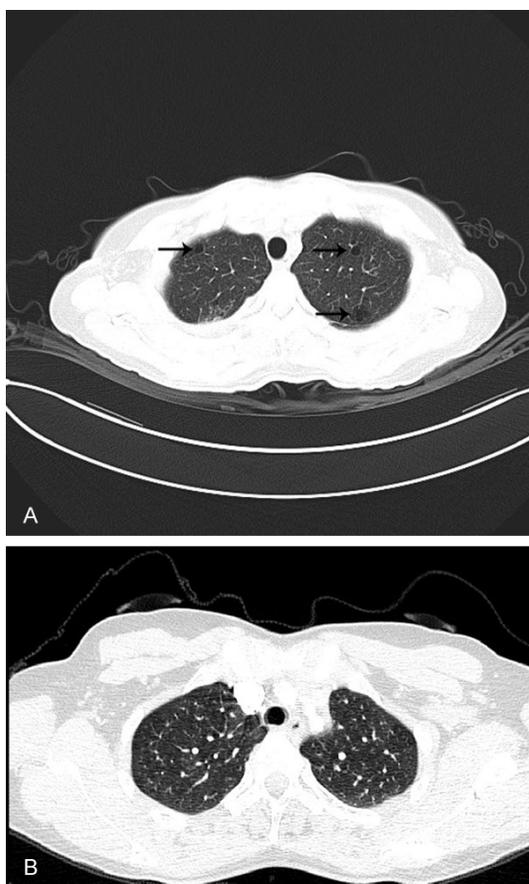


Figure 2. A. Chest computed tomography scan shows scattered thin-walled cysts (arrowheads) in the lungs. B. Chest computed tomography scan of a normal person.

cise testing may obtain additional information in patients with LAM but is more difficult to carry out because pneumothorax occurs during the testing [29]. Hypoxemia is common in the gases analysis of artery blood that has few benefit in LAM diagnosis. Nevertheless, arterial blood gas analysis is often used to evaluate oxygen therapy and lung transplantation and exclude hypocapnia.

Treatment

Lung function in patients with LAM declines continuously. This will lead to pulmonary failure even endanger the patient life. So far, the effect of medical therapy is poor and the options of treatments are limited (**Table 1**). Although the estrogen and (or) progesterone receptor can be detected by immunohistochemistry in about half of cases, the hormonal therapy has not obvious benefit for patients with LAM. Matrix

metalloproteinase 2 and 9 (MMP-2, MMP-9) are over-expressed in the lung specimens in patients with LAM, and the doxycycline can inhibit the production and activity of several MMPs (such as MMP-2 and MMP-9). However, there are very few evidences that doxycycline therapy has beneficial effects. Gratifyingly, mTOR may improve the lung function in patients with LAM. Moreover, for the advanced patients with LAM, lung transplantation is the definitive treatment option.

Lung transplantation

The LAM progresses continuously results in respiratory failure in the end. Therapeutic strategies, till recently, were very limited for patients with LAM. Lung transplantation has been the definitive treatment option for the advanced stage of LAM [30]. In 1984, it was the first time that Estenne reported the lung transplantation was treated successfully a LAM patient [31]. In an international survey, LAM occupied about one percent of all causes in heart or lung transplantations [32]. In 1983, it was the first published report of the treatment in patient with LAM by lung transplantation [33]. Early on, single lung transplantation was used in therapy of end-stage patients with LAM. The 1-, 3- and 5-year survival rates and the quality of life did no differ between the single-lung transplantation and the bilateral-lung transplantation. The interrelated specific operative complications have relations with autogeneic lung after single lung transplantation. The bronchiolitis obliterans syndrome has a relatively low morbidity rate after bilateral-lung transplantation; FEV₁ has a higher level as well. Therefore, it is the trend to take the bilateral lung transplantation as the better choice recently [32].

Doxycycline in treatment

Elevated serum concentrations of proteolytic enzymes (such as MMP2 and MMP9) have been found, and degradation of the extracellular matrix by these enzymes likely contributes to remodeling cystic lung tissue in patients with LAM [11, 34]. Doxycycline, a tetracycline antibiotic, can inhibit the production and activity of several MMPs. Pimenta et al. showed a decrease of urinary MMP-9 and serum MMP-2 in LAM patients treated with doxycycline (100 mg/day) [35]. Doxycycline also inhibits the growth and migration of tumor cell, lymphangio-

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Table 1. Trials of treatments of patients with LAM

Authors	Treatment	Type of study	Patients	Duration	Intervention	Resulting
Bissler et al. [50]	Sirolimus	Nonrandomized, open-label study.	5	24 months	Sirolimus for the first 12 months; Observation during the next 12-month.	Increased FEV ₁ and FVC. No significant change in D _{lco} .
Davies et al. [51]	Sirolimus	Phase 2 trial.	16	2 years	Oral sirolimus for up to 2 years.	Fell slightly in lung function. No changes in lung CT scan.
McCormack et al. [45]	Sirolimus	Randomized, double-blind trial.	89	24 months	Sirolimus group (46 patients); Placebo group (43 patients).	Increased FEV ₁ and FVC. No significant difference in D _{lco} or 6-MWD.
Taveira-DaSilva et al. [46]	Sirolimus	Observational study.	11	-	Treatment with sirolimus.	Increased FEV ₁ and D _{lco} .
Takada et al. [52]	Sirolimus	Single arm, open-label study.	63	2 years	Sirolimus for the first 12 months; Observation during the next 12-month.	Stabled FEV ₁ , FVC, and quality of life.
Jianhua et al. [53]	Sirolimus	Observational study.	38	5 years	Treatment with sirolimus.	Increased FEV ₁ and D _{lco} .
Neurohr et al. [54]	Sirolimus	Observational study.	10	6 months	Treatment with sirolimus.	Increased FEV ₁ and FVC.
Ando et al. [6]	Sirolimus	Observational study.	15	6 months	Treatment with sirolimus.	Increased FEV ₁ and FVC.
Goldberg et al. [55]	Everolimus	Multicentre, phase 2 trial.	24	26 weeks	Treatment with everolimus.	Increased FEV ₁ and 6-MWD. Stable FVC. Reduced serum VEGF-D and collagen IV.
Bissler et al. [56]	Everolimus	Double-blind, placebo controlled, phase 3 trial.	31	-	Everolimus group (22 patients); Placebo group (9 patients).	Increased FEV ₁ and D _{lco} .
Chang et al. [36]	Doxycycline	Randomized, placebo controlled trial.	23	21 months	Doxycycline group (12 patients); Placebo group (11 patients).	No significant difference in VC, gas transfer, or quality of life. Decreased MMP-9.
Pimenta et al. [37]	Doxycycline	Open-label, single-arm.	31	12 months	Treatment with doxycycline.	Decreased FEV ₁ and the minimum SpO ₂ . Increased 6-MWD. No significant change in D _{lco} .
Baldi et al. [49]	Bronchodilator	A randomized, double-blind, placebo-controlled, crossover trial.	38	3 days	Bronchodilator group (19 patients); Placebo group (19 patients).	Increasing in FEV ₁ . No increasing in FVC and TLC. Reduction in FEV ₁ /FVC ratio. No improvement in exercise tolerance.
Johnson et al. [57]	Progesterone	Observational study.	43	-	Treatment with progesterone.	Considerable variation in the rate of decline in FEV ₁ and TLCO.
Taveira-DaSilva et al. [58]	Progesterone	Observational study.	275	4 years	Progesterone (139 patients) No treatment (136 patients).	No difference in the rate of FEV ₁ decline.

FEV₁, forced expiratory volume in one second; VC, vital capacity; FVC, forced vital capacity; TLC, total lung capacity; D_{lco}, diffusing capacity of carbon monoxide; FRC, functional residual capacity; RV, residual volume; 6-MWD, six-minute walk distance; MMP-9, Matrix metalloproteinases-9.

genesis, and angiogenesis. However, studies on human LAM cells did not show the antiproliferative effect of doxycycline [36].

An open-label, single-arm, interventional clinical trial showed the significant decrease in FEV_1 and the insignificant increase in six-minute walk test, but no significant variation in D_{LCO} , after the treatment with doxycycline which was well tolerated in most patients [37]. The most frequent side effects, most were self-limited, included nausea, diarrhea, and epigastric pain. The another randomized, placebo-controlled, double-blind trial, which treated by doxycycline 100 mg/day for 3 months followed by 200 mg/day for 21 months or matched placebo, showed no effect upon FEV_1 , D_{LCO} , vital capacity, shuttle walk distance, or quality of life [36]. Moreover, more side effects were reported in the group by treatment with doxycycline. Although a small number of LAM patients got benefit from doxycycline, the therapeutic effects were indefinite.

Hormonal therapy

Because LAM occurs almost in women and LAM cells are known to express progesterone and oestrogen receptors unduly, hormonal factors have been considered to take part in the pathogenesis of LAM. Furthermore, some reports suggest that disease exacerbation in a cyclical pattern related to the menstrual cycle [38, 39]. There is a relatively stable condition in postmenopausal women with LAM as well. On the grounds of these observations, hormonal manipulation, especially progesterone, has been used for the treatment of patients with LAM for decades. Although many hormone therapeutic strategies were used as the treatment of LAM, there was no objective evidence to prove that anti-estrogen therapies can improve the patient condition. Gonadotrophin releasing hormone agonists (GnRH-A) may improve the condition in patients with LAM [40], but the relative clinical randomized controlled trial was not launched up to now. The oophorectomy was the first reported in the treatment of the LAM patients in 1979, and the most of patients got stable or better after an operation [41]. But in another observation showed that oophorectomy could not treat people or improve symptoms, and the disease even continued worse on its course [42]. The other hormonal therapy, such as progesterone and androgen, also achieve success in some case reports. However, no favorable consequences were consistently de-

monstrated in LAM patients with the treatment of hormonal therapy. In addition, the adverse reactions of hormonal therapy are well known, and there is no reason to expect that they would occur less. Because of the uncertain findings and the lack of a controlled clinical trial, hormone therapy in patients with LAM is not currently advocated [17].

The mTOR inhibitor

It is easy to know that drugs, which can inhibit the mTOR pathway, would be considered to avoid excessive proliferation of LAM cell. Rapamycin (sirolimus), an antibiotic, was described inhibitor of the mTOR pathway for the first time in 1975. It has made remarkable progress in the clinical anti-tumors research in the last decades. The mTOR complex consists of two distinct signaling complexes mTORC1 and mTORC2 in structure and function. Sirolimus can inhibit mTORC1, as is everolimus, by blocking the association of the FKBP12 with mTORC1 but not binding directly to FKBP12. It seems to be the mechanism of drug.

Other mTOR inhibitor analogues include everolimus, ridaforolimus and temsirolimus. They have also been developed. All the sirolimus analogues have the same central macrolide structure. However, different sirolimus analogues produce different bioavailability and half-life due to different compounds. Moreover, the second-generation mTOR inhibitors (also named ATP-competitive inhibitors) are in early clinical trials and show potent mTOR inhibition [43]. The first generation mTOR inhibitors, such as sirolimus and everolimus, proved mTORC1 inhibition, but the second generation produces both mTORC1 and mTORC2 inhibition, which may be more useful in the treatment of LAM [44]. Sirolimus was approved in the USA and everolimus was approved in Australia for the treatment of LAM.

The Multicenter International LAM Efficacy of Sirolimus (MILES) trial [45], a double blind placebo controlled parallel group study of sirolimus treated in LAM, presented that disease progression of LAM could slow down by intervened the mTOR pathway, and that mTOR inhibitor would be an effective medical treatment for LAM. The study showed that sirolimus could stabilize the lung function of patients with LAM. Sirolimus can also reduce the level of VEGF-D in serum, relieve the symptoms and improve

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the quality of life of patients with LAM [45]. In addition, the study also revealed that sirolimus may have therapeutic effects on patients with severe respiratory dysfunction, but not every patients with LAM. Although sirolimus caused more adverse reactions, severe adverse reactions did not increase. And there was a significant reduction in adverse reactions after withdrawal [45].

The MILES trial is the first randomized, controlled study to confirm that the drug has a therapeutic effect on LAM, and opens a new stage for successful treatment of LAM. Another observational trial shows that chylous fluid accumulations (pleural effusions and/or chylous ascites) in 12 patients with LAM had been resolved completely after beginning sirolimus therapy [46]. Based on these evidences, sirolimus was strongly recommended to treat patients with LAM with abnormal or declining lung function [17].

The adverse events associated with mTOR inhibitors therapy in LAM are often mild and primarily grade 1-2. The mTOR inhibitors were also reported well tolerated. Serious adverse events may occur as well, including peripheral oedema, cardiac failure, pneumonia and serious haematological abnormalities [45, 46]. These adverse reactions usually resolve with stopping taking the drugs. If the adverse events are severe, it is required to monitor as well. At present, it is only effective in LAM patients with obvious lung function damage [8]. Whether the mTOR inhibitors are effective for patients with the early stage of LAM, the evidence is still lacking. It is also a problem to be solved in the future research. The European guidelines for LAM clearly indicate that if the LAM patient's lung function continues to deteriorate, the use of rapamycin may be considered individually [8]. And the MILES study confirms that [45]. It should also be noted that rapamycin has not been approved for the treatment of LAM in some countries, and doctors and hospitals may not agree to prescribe the drug to patients with LAM [44].

Other treatment options

Owing to melanoma related antigens (gp-100), expressed by LAM cells, melanoma immunotherapy may be feasible for LAM despite adventurous. In addition, in the article of Klarquist

et al. underlines the general characteristics of cells responsible for LAM and melanoma tumors [47]. Therefore, vaccines against melanoma might be advantageous to LAM. A randomized trial showed that the patient got an increase in FEV₁ with the treatment of bronchodilator but no increase in FVC and TLC accompanied with a reduction in FEV₁/FVC ratio [48]. However, the results do not reflect an improvement in exercise tolerance in patients with LAM. More investigations were required to reveal whether patients benefit from treatment with bronchodilator in LAM. Moreover, mTORC₁ is an important inhibitor of autophagy, although not the unique one. Accordingly, mTORC₁ inhibition would promote abnormal proliferation of cell in LAM. It means that inhibitor of autophagy may provide new treatment options in LAM [49].

Conclusion

With the understanding of the pathogenesis of LAM, the targeted therapies will continue to be raised widely. Sirolimus were approved for LAM therapy and everolimus were approved for renal angiomyolipoma treatment in patients with LAM. Comparing to other drugs, mTOR inhibitors is an effective treatment for LAM, and the adverse effects are predictable. The treatment with mTOR inhibitors has promising results. Furthermore, extensive clinical trials are required to prove the validity of other possible treatment options, such as new estrogen blockers, inhibitors of autophagy and others.

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Disclosure of conflict of interest

None.

Abbreviations

LAM, Lymphangioleiomyomatosis; mTOR, mammalian target of rapamycin; TSC, tuberous scle-

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rosis complex; MMPs, Matrix metalloproteinases; D_{LCO} , diffusing capacity of the lung for carbon monoxide; VEGF-D, Vascular endothelial growth factor D; FEV₁, forced expiratory volume in 1 second; HRCT, high-resolution computed tomography; GnRH-A, Gonadotrophin releasing hormone agonists; FVC, forced expiratory volume.

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