Rapamycin for lymphangioleiomyomatosis: optimal timing and optimal dosage

Kai-Feng Xu,¹ Xinlun Tian,¹ Yanli Yang,¹ Hongbing Zhang²

Lymphangioleiomyomatosis (LAM) occurs predominantly in women in one of two forms: sporadic LAM and LAM associated with the autosomal dominant genetic disease tuberous sclerosis complex (TSC). Its clinical presentation includes dyspnoea, pneumothorax, chylothorax and renal angiomyolipoma. Many patients exhibit mild symptoms at the time of diagnosis, and their lung function then gradually declines. In the end-stage of LAM, lung transplantation is the only option. Due to mutations of either TSC1 or TSC2 gene, aberrant activation of mammalian/mechanistic target of rapamycin (mTOR) causes TSC and/or LAM.^{1,2} There were no effective therapeutics for LAM until the mTOR inhibitor rapamycin (sirolimus) exhibited efficacy in an open-label study published in 2008.³ The efficacy of this drug was confirmed in the randomised, double-blinded Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus (MILES) trial.⁴ Primarily based on findings from the MILES study, sirolimus has been approved for the treatment of LAM in Japan and USA. In recent guidelines for LAM issued by the American Thoracic Society and the Japanese Respiratory Society, rapamycin is recommended for patients with reduced lung function.⁵

A real-world observational study by Bee and colleagues that appears in *Thorax* expanded our knowledge regarding two important questions: when and how much rapamycin could be used to treat LAM.⁶ In a prospective cohort comprising 47 patients during a 3-year follow-up, the authors found that (1) patients with LAM with a shorter duration of disease and less severely impaired lung function responded better to rapamycin; (2) different dosages of rapamycin produced similar benefits

and (3) lower doses had fewer side effects. Therefore, early treatment with low-dose rapamycin may better preserve lung function with less side effects.⁶

When should we start rapamycin for patients with LAM? In the 2016 guidelines, rapamycin was recommended for those who exhibit reduced lung function, which was defined as less than 70% of the predicted forced expiratory volume in 1 s (FEV₁).⁵ Although Bee and colleagues examined a small cohort, their data suggest that rapamycin treatment may better preserve lung function for patients who are treated earlier and exhibit less impaired lung function. However, MILES study suggested that severe patients with higher levels of vascular endothelial growth factor-D (VEGF-D) might benefit more from rapamycin.⁷ Multiple factors may influence the decision of beginning treatment.⁸ Future studies are needed to build a prediction model of treatment response based on clinical, radiological, biomarker and molecular characteristics. For example, patients with lymphatic involvement, such as chylothorax^{9–11} or renal angiomyolipoma,³ may be more likely to benefit from rapamycin. On the other hand, patients with a slow progress clinically, for example, CT stage I–II LAM or postmenopausal women may be more likely to be observed rather than to be treated. Because of multiorgan involvement in TSC, TSC-associated LAM may require treatment with mTOR inhibitors even if the lung lesion is mild. The value of VEGF-D in diagnosis and management should be determined.^{7,8,10}

What is the treatment option for patients with at least 70% predicted FEV₁? In the 2016 guidelines, patients with a rapid decline in FEV₁, which was proposed as a decrease of 90 mL per year, could be considered for treatment.⁵ We have no answers regarding whether the following types of patients should be treated: (1) patients with normal and stable FEV₁ and (2) patients with normal FEV₁ and abnormal diffusion capacity. Intuitively, most of the patients with LAM may be treated with rapamycin once they are diagnosed to prevent further destruction of normal

lung tissues by LAM cells. Due to issues related to a lack of supporting evidence, cost, long-term use and safety concerns, observation is often recommended for asymptomatic patients with normal or mildly impaired lung function.

Dosage of rapamycin for LAM was initially derived from the triple-drug regimen to prevent immune rejection of transplanted kidneys. In the MILES study, the target trough concentration of rapamycin was 5–15 ng/mL,⁴ which is usually recommended for kidney transplantation. Clinically, few patients exhibit rapamycin concentrations greater than 10 ng/mL. The dose–response curve for rapamycin remains unknown. Bee and colleagues divided patients quarterly and found that different concentration levels produced similar effects.⁶ Lower dosages produced similar treatment responses with fewer side effects. Because of the quite limited number of patients in each quarter, their observation has to be interpreted with caution. If this observation is confirmed in large-scale studies, rapamycin should be recommended at a lowest effective dosage because the examined range of dosages revealed no dose–response relationship. In a report that described 15 patients with rapamycin concentrations of less than 5 ng/mL, the treatment response was similar to the ones described in previous reports.¹² The mean concentration was 2.16 ng/mL (range 0.8–4.3 ng/mL), indicating that rapamycin could be administered at much lower doses than previously thought. In our own experience, we use 5–10 ng/mL as our targeted concentration, and approximately 20% of patients have concentrations less than 5 ng/mL (unpublished data). We adjust rapamycin dosage based on treatment stage (initial treatment or maintenance), complications (chylothorax, angiomyolipoma, pulmonary hypertension or TSC), treatment response, side effects and blood concentration. We prefer to use relatively low doses for patients with lung involvement only, stable lung function or patients in the maintenance phase. The question of what the lowest optimal dose of rapamycin is for LAM should be addressed.

The safety data reported by Bee and colleagues⁶ were consistent with data from previous reports. Side effects of rapamycin are typically mild and tolerable. Common side effects of rapamycin include oral ulcer, acne, irregular menses, infection and hyperlipidaemia. Rapamycin-induced pneumonitis has also been reported.^{11,13} Because rapamycin has been used as an immunosuppressant for organ transplantation, patients and physicians are often

¹Department of Respiratory Medicine, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China

²Department of Physiology, Institute of Basic Medical Sciences, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China

Correspondence to Dr Kai-Feng Xu, Department of Respiratory Medicine, Peking Union Medical College Hospital, Beijing, China; xukf@pumch.cn

Table 1 Summary of rapamycin (sirolimus) trials for LAM

Year	Type of study	Sample size	Intervention	Drug levels	Duration	Effects
2008 ³	Open label	11 (LAM) 20 (AML)	Sirolimus	10–15 ng/mL except one case	12 m treatment 12 m observation	↑ FEV ₁ , FVC ↓ AML size
2011 ^{4,7}	Randomised, double blind	89	Sirolimus versus placebo	5–15 ng/mL	12 m treatment 12 m observation	↑ FEV ₁ , FVC, QoL, functional performance ↓ VEGF-D, FRC, air trapping ↔ 6MWD, DLCO
2011 ⁹	Observation	19	Sirolimus	5–15 ng/mL	2.6±1.2 years	↑ FEV ₁ , FVC, DLCO ↓ Chylothorax volume
2011 ¹³	Observation	10	Sirolimus	5–10 ng/mL	12.1±2.8 m	↑ FEV ₁ , FVC, 6MWD, DLCO ↔ TLC, PaO ₂
2011 ¹⁸	Open label	16	Sirolimus	3–10 ng/mL	24 m	↓ AML size ↔ FEV ₁ , FVC, DLCO
2013 ¹²	Retrospective	15	Sirolimus	2.16 (0.8–4.3) ng/mL	17.5±5.9 m without chylothorax 12.0±5.5 m with chylothorax	↑ FEV ₁ , FVC ↓ VEGF-D, chylothorax
2014 ¹⁹	Observation	38	Sirolimus	5–15 ng/mL	3.4±2.4 years; 5 years in 12 patients	↑ FEV ₁ , DLCO ↔ Cysts, 6MWD
2015 ²⁰	Retrospective	78	Sirolimus, simvastatin or combined		Mean 2.7–2.8 years	↑ FEV ₁ , DLCO ↔ No effects from adding simvastatin
2016 ¹¹	Open label	63	Sirolimus	5–15 ng/mL	24 m	↑ FEV ₁ , FVC in a chylothorax subgroup ↔ QoL, FEV ₁ , FVC
2016 ¹⁰	Observation	25	Sirolimus	5–15 ng/mL	4.5±1.6 years	↓ Chylothorax, VEGF-D, AML size ↔ FEV ₁ , DLCO

6MWD, 6 min walk distance; AML, angiomyolipoma; DLCO, diffusing capacity of the lung for carbon monoxide; FEV₁, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; LAM, lymphangioleiomyomatosis; m, months; QoL, quality of life; RV, residual volume; TLC, total lung capacity; TSC, tuberous sclerosis complex; VEGF-D, vascular endothelial growth factor-D; ↑, improved or increased in size or value; ↓, worsened or decreased in size or value; ↔, similar or unchanged.

concerned of potential pulmonary or other infections as a result of immunosuppression. However, in the randomised MILES trial, no rapamycin-associated increases in pulmonary or other infections were observed.⁴

One reasonable approach would be to prescribe rapamycin early for an indicated population to preserve lung function and reduce side effects. Future studies are required to generate a prediction model for rapamycin response and drug safety to guide precise and individualised therapy. In the Multicenter Interventional Lymphangioleiomyomatosis Early Disease (MILED) trial, patients with FEV₁ greater than 70% of the predicted value will receive a fixed dose of 1 mg per day of rapamycin or placebo for 2 years (NCT03150914). This type of clinical trial is designed to address early treatment with a low dose of rapamycin.

Notably, subsets of patients treated with rapamycin continue to lose lung function at an accelerated rate. The question of why certain patients are resistant or less responsive to rapamycin remains unresolved. The irreversible replacement of lung parenchyma with LAM lesions is largely responsible for declines in lung function. Furthermore, rapamycin is primarily a cytostatic but not a cytotoxic inhibitor. Adjunctive therapy may be developed to improve the efficacy of rapamycin. The combined inhibition of

mTOR and autophagy is being assessed in a clinical trial.¹⁴ Since mTOR active cells are vulnerable to disruption of their dependence upon aerobic glycolysis (Warburg effect) and glutaminolysis, combined suppression of either mTOR and glycolysis or glutamine metabolism and glycolysis was proposed, respectively, for treatment of TSC, LAM and other hyperactive mTOR-related diseases.^{15,16} A recent study suggests that guanylate nucleotide synthesis inhibitor mizoribine may be repurposed to treat TSC or LAM.¹⁷

Clinical studies of rare diseases such as LAM are typically limited by sample size. Only a few thousand patients with LAM are registered in LAM research networks worldwide. Nevertheless, multiple clinical trials have been conducted based on the connections of TSC1/TSC2 gene mutations and mTOR activation in TSC and LAM,^{1,2} and fascinating progress has been achieved with respect to the treatment of LAM with rapamycin (table 1). When evidence has been accumulated, care for patients with LAM will be optimised.

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