Efficacy and safety of low-dose Sirolimus in Lymphangioleiomyomatosis

Hee-Young Yoon¹, Jung Jin Hwang², Dong Soon Kim¹ and Jin Woo Song¹*

Abstract

Background: Lymphangioleiomyomatosis is a rare disease caused by unregulated activation of mammalian target of rapamycin (mTOR) signalling pathway. Sirolimus showed efficacy in a phase 3 trial of patients with lymphangioleiomyomatosis, but the optimal dose remains unclear.

Methods: We investigated the efficacy and safety of low-dose compared with conventional-dose sirolimus. Clinical data of 39 patients with lymphangioleiomyomatosis (mean age, 34.8 years; median treatment period, 29.6 months) who received sirolimus were retrospectively reviewed. Low-dose sirolimus was defined as any dose that maintained mean blood trough levels lower than those maintained with conventional doses (5–15 ng/mL).

Results: Fifty-one percent of patients received low-dose therapy. The rate of decline in lung function decreased after treatment in the whole group (forced expiratory volume in 1 s [FEV₁], −0.12 ± 0.47 [before] vs. 0.24 ± 0.48% predicted/month, p = 0.027; diffusing capacity for carbon monoxide [DLco], −0.33 ± 0.61 vs. 0.03 ± 0.26% predicted/month, p = 0.006) compared with before treatment. In the low-dose group, the rate of decline in FEV₁ (−0.08 ± 0.38 [before] vs. 0.19 ± 0.51% predicted/month [after], p = 0.264) and DLco (-0.13 ± 0.62 vs. 0.02 ± 0.28% predicted/month, p = 0.679) showed a numeric trend towards improvement after treatment; however, the conventional-dose group showed significant improvement in FEV₁ (−0.26 ± 0.54 [before] vs. 0.22 ± 0.38 [after] % predicted/month, p = 0.024) and DLco (−0.55 ± 0.58 vs. 0.04 ± 0.25% predicted/month, p = 0.002) after treatment. Adverse events (AEs) occurred in 89.7% of patients and the most common AEs was hypercholesterolaemia (43.6%), followed by stomatitis (35.9%). The occurrences of AE were similar between the low- and conventional-dose groups (85.0% vs. 94.7%, p = 0.605).

Conclusions: Low-dose sirolimus may stabilise lung function decline in lymphangioleiomyomatosis patients, but its efficacy appears to be inferior to that of conventional-dose sirolimus.

Keywords: Lymphangioleiomyomatosis, Sirolimus, Low dose, Respiratory function tests, Treatment outcome

Background

Lymphangioleiomyomatosis (LAM) is a rare progressive lung disease that mainly affects women of child-bearing age [1, 2]. The disease occurs sporadically or in association with tuberous sclerosis complex (TSC), and both are characterised by smooth muscle cell infiltration, cystic lung destruction, systemic angiomyolipoma (AML) and lymphangioleiomyoma formation [2, 3]. LAM is caused by mutations in the tuberous sclerosis genes, resulting in activation of the mammalian target of the rapamycin complex 1 (mTORC1) signalling network [4], a protein kinase that controls cell growth, proliferation and survival, and contributes to the uncontrolled proliferation of LAM cells [5]. Sirolimus, a highly specific inhibitor of mTORC1, can suppress the growth of spontaneously occurring renal tumours in a Tsc2−/− Eker rat model [6] and in Tsc1+/− and Tsc2−/− mice [7], as well as in TSC2-deficient xenograft tumours in immune-deficient mice [8].

Based on early preclinical data, trials of sirolimus therapy in human tuberous sclerosis or LAM have been performed [9–11]. In a phase 3 trial of patients with LAM, sirolimus improved lung function, quality of life and functional performance [10]. In that study, the blood trough level of sirolimus was maintained between 5 and

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15 ng/mL, based on a previous phase 1–2 trial [9]. However, the optimal treatment dose was not given because a significant number of patients developed problematic side effects, such as stomatitis, and the potential risk of developing a malignant tumour increased with long-term use [12]. In a recent study, low-dose sirolimus treatment (trough level < 5 ng/mL) was shown to improve lung function in nine patients without chylous effusion and to resolve chylothoraces in seven patients with chylous effusions [13]. That study was limited by the small number of patients and the absence of comparison with conventional-dose therapy. Therefore, we aimed to compare the efficacy and safety of low- and conventional-dose sirolimus in patients with LAM.

Materials and methods
Study population
The present study included 39 patients with LAM (82.1% biopsy-proven cases) treated with sirolimus between May 2011 and March 2016 at Asan Medical Center, Seoul, Republic of Korea (Fig. 1). All subjects met the diagnostic criteria of the American Thoracic Society/Japanese Respiratory Society guideline [14]. Subjects treated with sirolimus, who had mean blood trough levels maintained < 5 ng/mL, were classified as the low-dose sirolimus group. Informed consent was waived, and the study was approved by the Asan Medical Center Institutional Review Board (2016–0480).

Methods
Clinical and survival data for all patients were retrospectively obtained from medical records, telephone interviews and/or National Health Insurance records. All subjects were routinely follow-up at 3-month intervals, and pulmonary function tests and measurement of blood sirolimus levels were performed at each follow-up visit. Whole blood sirolimus levels were measured by liquid chromatography-tandem mass spectrometry (LC-MS). Spirometry and measurement of the diffusing capacity of the lung for carbon monoxide (DLco) were performed according to the recommendations of the American Thoracic Society (ATS) and European Respiratory Society, and the results were expressed as percentages of normal predicted values [15–17]. The six-minute walk test was performed according to ATS guidelines [18].

Evaluation of efficacy and safety
Efficacy was evaluated in patients who were treated with sirolimus for more than 12 weeks and who underwent pulmonary function tests more than three times before and after treatment (Fig. 1). Changes in lung function, specifically, forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and DLco, from baseline to 12 or 24 months before and after treatment were evaluated. The rate of decline in lung function was estimated by linear regression modelling and compared before and after treatment. For categorical comparison, disease progression was defined as any decline in FEV1 during the observation period. The treatment response of extra-pulmonary manifestations was assessed in patients with AML or lymphangioma who had follow-up CT images using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria (version 1.1) [19] and classified as follows: complete response (completely disappeared tumor),...

Fig. 1 Flowchart of patients included from the analysis
partial response (≥ 30% decrease in the sum of longest diameters of target lesions), progression (≥ 20% increase in the sum of longest diameters), and stability (all other changes). In this study, complete or partial responses were regarded as ‘improvement’.

Safety was evaluated in all patients who received at least one dose of sirolimus (Fig. 1). AEs were identified from the initiation of treatment to 28 days after the last dose and were classified using the preferred terms in the Common Terminology Criteria for Adverse Events (Version 4.0). SAEs were defined as any AEs occurring with any dose that resulted in any of the following outcomes: death, hospitalisation for life-threatening causes, disability or permanent damage, intervention to prevent permanent impairment or damage, or other serious medical events.

**Statistical analysis**
All values are reported as mean ± standard deviation (SD) for continuous variables or as percentages for categorical variables. Student’s *t*-test and the Mann–Whitney U test were used for continuous data, and Pearson’s chi-square test and Fisher’s exact test were used for categorical data. Comparison of the rate of lung function decline and changes in lung function before and after treatment were performed by unpaired *t*-tests with or without Welch’s correction, as appropriate. All statistical analyses were performed using IBM SPSS, Version 21.0 (IBM Corp., Armonk, NY, USA). A two-tailed *p*-value < 0.05 was considered to indicate statistical significance.

**Results**
**Baseline characteristics of the subjects**
Of the total of 39 patients, 51% were classified as receiving low-dose treatment. The median treatment period was 29.6 months (29.2 months in the low-dose group vs. 30.0 months in the conventional-dose group, *p* = 0.261), and mean blood sirolimus level was 5.5 ± 2.8 ng/ml (3.5 ± 1.3 ng/ml in the low-dose group vs. 7.7 ± 2.3 ng/ml in the conventional-dose group, *p* = 0.001). In the low-dose group, the mean trough level of sirolimus was maintained below 5 ng/ml during the treatment period (Additional file 1: Figure S1). There were no differences between the low- and conventional-dose groups in age, gender, smoking history, prior treatment, extrapulmonary manifestations, lung function or exercise capacity (Table 1). However, more subjects in the low-dose group had TSC (30.0% vs. 0.0%, *p* = 0.020). Most subjects in the low-dose group maintained low blood trough levels due to adverse events (AEs, 67.5%) or a stable disease course after initial treatment (25.0%) (Additional file 2: Table S1). Among patients with TSC-LAM (*n* = 6), four received low-dose sirolimus due to azotaemia (*n* = 1) and treatment history of the renal procedure due to AML (*n* = 3) and remaining two did due to mucositis.

**Changes in lung function**
In the whole group, changes in FEV 1 significantly improved 12 and 24 months after treatment (ΔFEV 1, 3.4 ± 9.3% predicted at 12 months, *p* = 0.004; 6.9 ± 11.5% predicted at 24 months, *p* = 0.007) compared with those before treatment (ΔFEV 1, − 4.2 ± 8.2% predicted; Fig. 2a). The changes in DLco also exhibited similar trends after treatment (ΔDLco, 3.1 ± 7.7% predicted at 12 months, *p* = 0.006; 2.4 ± 8.0% predicted at 24 months, *p* = 0.032; Fig. 2b). By contrast, FVC only showed a numerical improvement after treatment (ΔFVC, 3.1 ± 7.7% predicted at 12 months, *p* = 0.250; 6.8 ± 14.8% predicted at 24 months, *p* = 0.582; Fig. 2c).

In the low-dose group, FEV 1 showed an improving trend at 12 and 24 months after treatment (ΔFEV 1, 4.2 ± 11.6% predicted at 12 months, *p* = 0.169; 7.2 ± 12.0% predicted at 24 months, *p* = 0.212) without statistical significance (Fig. 2a). DLco (ΔDLco, 6.6 ± 14.0% predicted at 12 months, *p* = 0.145; 6.6 ± 14.0% predicted at 24 months, *p* = 0.250) and FVC (ΔFVC, 3.4 ± 10.7% predicted at 12 months, *p* = 0.283; 2.7 ± 11.1% predicted at 24 months, *p* = 0.891) also showed similar trends (Fig. 2b and c). On the other hand, the conventional-dose group showed significant improvements in FEV 1 (ΔFEV 1, 2.7 ± 7.0% predicted at 12 months, *p* = 0.010; 6.6 ± 11.7% predicted at 24 months, *p* = 0.015; Fig. 2a) and DLco (ΔDLco, 2.8 ± 3.7% predicted at 12 months, *p* = 0.001; 2.1 ± 2.6% predicted at 24 months, *p* = 0.010; Fig. 2b) at 12 and 24 months after treatment; however, only numerical improvements in FVC were observed after treatment (ΔFVC, 2.2 ± 5.9% predicted at 12 months, *p* = 0.608; 6.9 ± 6.5% predicted at 24 months, *p* = 0.233; Fig. 2c). There were no differences between the two groups in changes in lung function (FEV 1, FVC and DLco) before and after treatment.

**Rate of decline in lung function**
In the whole group, the rate of decline in FEV 1 was significantly reduced after treatment (− 0.12 ± 0.47% predicted/month [before] vs. 0.24 ± 0.48% predicted/month [after], *p* = 0.027) compared with before treatment (Additional file 3: Table S2). The rate of decline in DLco (− 0.33 ± 0.61% predicted/month [before] vs. 0.03 ± 0.26% predicted/month [after], *p* = 0.006) was also reduced after treatment, but that of FVC was not.

In the low-dose group, the rate of decline in FEV 1 showed an improving trend after treatment (− 0.08 ± 0.38% predicted/month [before] vs. 0.19 ± 0.51% predicted/month [after], *p* = 0.264) without statistical significance (Additional file 3: Table S2). There were similar trends in the rates of decline in FVC and DLco.
Table 1: Comparison of baseline characteristics between the low-dose and conventional-dose groups

| Characteristic                              | Total   | Low-dose | Conventional-dose |
|--------------------------------------------|---------|---------|-------------------|
| Number of patients                         | 39      | 20      | 19                |
| Age, years                                 | 34.8 ± 8.3 | 34.0 ± 8.7 | 35.6 ± 8.1        |
| Female                                     | 39 (100.0) | 20 (100.0) | 19 (100.0)        |
| Smoking                                    |         |         |                   |
| Never                                      | 36 (92.3) | 19 (95.0) | 17 (89.5)         |
| Former                                     | 3 (7.7)  | 1 (5.0)  | 2 (10.5)          |
| Current                                    | 0 (0.0)  | 0 (0.0)  | 0 (0.0)           |
| TSC                                        | 6 (15.4) | 6 (30.0)* | 0 (0.0)           |
| Postmenopausal state                       | 2 (5.1)  | 1 (5.0)  | 1 (5.3)           |
| Previous treatment                         |         |         |                   |
| Medroxyprogesterone                        | 14 (35.9) | 7 (35.0)  | 7 (36.8)          |
| LHRH                                       | 4 (10.3) | 1 (5.0)  | 3 (15.8)          |
| Bilateral oophorectomy                     | 1 (2.6)  | 1 (5.0)  | 0 (0.0)           |
| History of extrapulmonary manifestation    |         |         |                   |
| Pneumothorax                               | 24 (61.5) | 15 (75.0) | 9 (47.4)          |
| Angiomyolipoma                             | 14 (35.9) | 9 (45.0)  | 5 (26.3)          |
| Lymphangioleiomyoma                        | 5 (12.9) | 1 (5.0)  | 4 (21.1)          |
| Chylothorax                                | 3 (7.7)  | 2 (10.0) | 1 (5.3)           |
| Lung function                              |         |         |                   |
| FEV₁, % predicted                          | 67.7 ± 26.4 | 62.9 ± 27.4 | 72.3 ± 2.3        |
| FVC, % predicted                           | 86.2 ± 14.9 | 83.3 ± 13.8 | 88.9 ± 15.7       |
| DLco, % predicted                          | 51.7 ± 21.8 | 52.6 ± 23.1 | 50.9 ± 21.2       |
| FEV₁/FVC ratio                             | 66.2 ± 20.8 | 64.1 ± 2.4  | 68.2 ± 17.6       |
| 6MWT                                       |         |         |                   |
| Distance, meter                            | 456.9 ± 103.6 | 458.4 ± 103.5 | 455.1 ± 106.9   |
| Initial SaO₂, %                            | 97.6 ± 1.7  | 97.7 ± 1.7  | 97.6 ± 1.7        |
| Lowest SaO₂, %                             | 93.7 ± 4.7  | 94.5 ± 4.9  | 92.8 ± 4.5        |
| Sirolimus level, ng/mL                     | 5.5 ± 2.8   | 3.5 ± 1.3*  | 7.7 ± 2.3         |

Data are presented as mean ± SD or number (%)

Abbreviations: TSC tuberous sclerosis complex, LHRH luteinising hormone-releasing hormone, FEV₁ forced expiratory volume in 1 s, FVC forced vital capacity, DLco diffusing capacity of the lung for carbon monoxide, 6MWT six-minute walk test, SaO₂ oxygen saturation

*P < 0.05 (compared with conventional-dose group)

Fig. 2: Changes in lung function before and after treatment. Changes in FEV₁ (A), DLco (B) and FVC (C) before and after treatment. Bars and lines show the mean ± standard error of changes in lung function. Abbreviations: Pre_12M, 12 months before treatment; Post_12M, 12 months after treatment; Post_24M, 24 months after treatment; FEV₁, forced expiratory volume in 1 s; DLco, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity. *p < 0.05
after treatment. However, in the conventional-dose group, the rates of decline in FEV₁ (−0.26 ± 0.54% predicted/month vs. 0.22 ± 0.38% predicted/month, \( p = 0.024 \)) and DLco (−0.55 ± 0.58% predicted/month vs. 0.04 ± 0.25% predicted/month, \( p = 0.002 \)) were significantly reduced after treatment (Additional file 3: Table S2).

**Disease progression**

In the whole group, the rate of disease progression, which was defined as any decline in FEV₁, decreased after treatment (77% before vs. 33% at 12 months [\( p = 0.008 \)] vs. 35% at 24 months [\( p = 0.024 \)] ) (Fig. 3a). In the low-dose group, the rate of disease progression showed a trend towards decrease after treatment (63% before vs. 43% at 12 months [\( p = 0.659 \)] vs. 44% at 24 months [\( p = 0.637 \)] ) (Fig. 3b). In the conventional-dose group, however, the rate of disease progression decreased significantly after treatment (100% before vs. 25% at 12 months [\( p = 0.006 \)] vs. 25% at 24 months [\( p = 0.021 \)] ) (Fig. 3c).

**Treatment response of extra-pulmonary manifestations**

Among 18 patients with extra-pulmonary manifestations, 11 (61.1%) were assessed for treatment responses. The median observation time from the initiation of sirolimus to the last CT follow-up during treatment was 2.9 years (range: 1.4–5.8 years; 2.8 [low] vs. 3.1 [conventional] years, \( p = 0.631 \)). In the whole group, five (45.5%) patients showed improvement and 6 (54.5%) showed stability. Comparison of the results between the low and conventional groups were similar; in the low-dose group, improvement and stability were observed in 2 (28.6%) and 5 patients (71.4%), respectively and in the conventional-dose group, those were observed in 3 (75.0%) and 1 patients (16.7%), respectively (\( p = 0.242 \)).

**Adverse events**

Of all patients, 89.7% experienced AEs, averaging 3.46 AEs per patient (Table 2 and Additional file 4: Table S3). The most common AE was hypercholesterolaemia (43.6%), followed by stomatitis (35.9%). The rate of AEs in the low-dose group did not differ from that in the conventional-dose group (85.0% vs. 94.7%, \( p = 0.605 \)). Although there were no significant differences in AEs between the groups, the most common AE in the low-dose group was stomatitis (50.0%), whereas hypercholesterolaemia was the most common in the conventional-dose group (52.6%). The rate of AEs per patient was also comparable in the two groups (3.70 events per patient in the low-dose group and 3.21 events per patient in the conventional-dose group, \( p = 0.406 \)) (Additional file 4: Table S3).

Serious adverse events (SAEs) occurred in 17.9% of all subjects, and there was no significant difference in the rate of SAEs between the low- and conventional-dose groups (15.0% vs. 21.0%, \( p = 0.695 \)) (Table 2). Although there were no significant differences in the rate of AEs between the groups, the most common SAEs were infection (15.0%) in the low-dose group and pneumothorax (10.5%) in the conventional-dose group. There were no deaths during follow-up.

**Discontinuation of treatment**

Seven patients (17.9%) permanently discontinued treatment due to planned pregnancy (7.7%), AEs (5.1%), or stable disease status (1.1%). Although the overall discontinuation rate was lower in the low dose group (5.0% [low] vs. 31.6% [conventional], \( p = 0.044 \)) than in the conventional dose group, the discontinuation rate due to AEs were not different between two groups (5.0% vs. 5.3%, \( p = 1.000 \); Additional file 5: Table S4). Of the two patients who discontinued sirolimus due to AEs, one in the low-dose group discontinued because of stomatitis and one in the conventional-dose group discontinued due to stomatitis and urticaria.

**Discussion**

In our current study, low-dose sirolimus may stabilise lung function decline in patients with LAM. The rates of...
Table 2 Comparison of adverse events and serious adverse events between the low-dose and conventional-dose groups

| Type of event          | Total  | Low-dose | Conventional-dose |
|------------------------|--------|----------|-------------------|
| Number of patients     | 39     | 20       | 19                |
| Adverse events         | 35 (89.7) | 17 (85.0) | 18 (94.7)         |
| Hypercholesterolaemia  | 17 (43.6) | 7 (35.0)  | 10 (52.6)         |
| Stomatitis             | 14 (35.9) | 10 (50.0)* | 4 (21.1)          |
| URI                    | 9 (23.0)  | 3 (15.0)  | 6 (31.6)          |
| Diarrhoea              | 7 (17.9)  | 4 (20.0)  | 3 (15.8)          |
| Headache               | 5 (12.8)  | 4 (20.0)  | 1 (5.3)           |
| Vaginal bleeding       | 5 (12.8)  | 1 (5.0)   | 4 (21.1)          |
| Acneiform lesions      | 4 (10.3)  | 3 (15.0)  | 1 (5.3)           |
| UTI                    | 4 (10.3)  | 2 (10.0)  | 2 (10.5)          |
| Serious adverse events | 7 (17.9)  | 3 (15.0)  | 4 (21.1)          |
| Infection*             | 4 (10.3)  | 3 (15.0)  | 1 (5.3)           |
| Pneumothorax           | 3 (7.7)   | 1 (5.0)   | 2 (10.5)          |
| Malignancy**           | 1 (2.3)   | 0 (0.0)   | 1 (5.3)           |

Data are presented as number (%)  
Abbreviations: URI upper respiratory infection, UTI urinary tract infection  
*P < .1 (compared with conventional-dose group)  
*Infection included pneumonia (n = 3) and cellulitis (n = 1)  
**Thyroid cancer

Figure 1 (not provided)

The proportion of patients with TSC-LAM was greater in the low-dose group than in the conventional-dose group. These findings might be attributed from frequent renal involvement in patients with TSC-LAM, such as AML, renal cyst and renal-cell carcinoma. Because of renal complications, these patients tend to undergo nephrectomy or embolisation more frequently [24]. In our cohort, four of six patients with TSC-LAM underwent renal procedures including embolisation and nephrectomy. Because sirolimus has the potential to exacerbate pre-existing or newly occurring renal lesions by causing massive proteinuria, glomerulonephritis or thrombotic microangiopathy [25], patients with TSC who already have impaired renal function might prefer low-dose sirolimus therapy. Actually, most patients with TSC-LAM in our cohort received low-dose sirolimus due to a potential risk of renal impairment and showed the stable course of lung function changes without discontinuation after treatment.

In the present study, the rates of infection, including upper respiratory infection (23.0% vs. 44.0%), urinary tract infection (10.3% vs. 16.0%) and cellulitis (2.5% vs. 12.0%), were lower than those in a study by Bissler et al. [9]. In particular, the incidence of pneumonia requiring hospitalisation in our total cohort was also lower than that in another study (7.7% vs. 30.0%) [26]. Although sirolimus did not increase the risk of infection compared with the placebo in phase 3 clinical trial involving patients with LAM [10], considering the increased risk of infection with sirolimus treatment in transplant patients [27, 28], these results were probably due to the effect of low-dose sirolimus. The rates of stomatitis (35.9% vs. 68.0%) and diarrhoea (17.9% vs. 28.0%) were also lower in our study than in a conventional-dose study [9]; however, the rate of hypercholesterolaemia in our total subjects was similar to that in patients receiving conventional doses of sirolimus in other studies (43.6% vs. 42.1–52.0%) [9, 29].

The AE rates were comparable between the two treatment groups in our study, although the rate of stomatitis showed a trend towards being higher in the low-dose group. However, it should be noted that this was a retrospective study, and most patients who were included in the low-dose group had maintained low doses due to AEs, including mostly stomatitis. Nevertheless, the majority of patients with AEs continued sirolimus with conservative dose...
therapy, resulting in comparable AE-related discontinuation rates between the two groups (5% [low dose] vs. 5.3% [conventional dose], \( p = 1.000 \)). These findings indicate that the AEs in the low-dose group were not severe enough to cause discontinuation of treatment. Thus, low-dose sirolimus can be considered tolerable for patients who experience AEs while taking conventional doses.

Our study has some important limitations. First, the number of patients included was relatively small, especially for analysis of efficacy in each group. This is related to the lack of statistical significance in subgroup analysis. However, our results showed that the reduction in lung function before treatment was changed to an increase in lung function after treatment in both groups. Second, this was a retrospective study conducted in a single tertiary referral centre; however, the demographics and lung function of our patients were comparable to those in other studies. Finally, the proportion of patients with TSC-LAM was higher in the low-dose group than in the conventional-dose group. Nevertheless, baseline lung function did not differ between the two groups, and a recent study showed that there were no differences in changes of FEV\(_1\), DLco and cyst scores between patients with TSC-LAM and those with sporadic LAM [30]. Therefore, the difference in the proportion of patients with TSC-LAM between two groups would not affect the results of lung function analysis.

**Conclusions**

In conclusion, our data suggest that low-dose sirolimus may stabilise lung function decline in patients with LAM who have moderately impaired lung function, and that low-dose sirolimus may be less effective than conventional-dose therapy in preventing lung function decline and disease progression. Based on our results, low-dose sirolimus could be considered a treatment option in patients with LAM, especially those who suffer from intolerable AEs or who have a long-term stable course. Further prospective studies are warranted to confirm these findings.

### Additional files

- **Additional file 1**: Figure S1. The mean blood trough level of sirolimus during the first two years of treatment. Dots and error bars show the mean ± 95% confidential interval (DOCX 13 kb)
- **Additional file 2**: Table S1. Reasons to maintain low-dose sirolimus treatment. (DOCX 18 kb)
- **Additional file 3**: Table S2. Comparison of the rates of decline in lung function between the low-dose and conventional-dose groups. (DOCX 19 kb)
- **Additional file 4**: Table S3. Comparison of adverse events and serious adverse events between the low-dose and conventional-dose groups. (DOCX 19 kb)
- **Additional file 5**: Table S4. Comparison of reasons for treatment discontinuation between the low-dose and conventional-dose groups (DOCX 13 kb)

### Abbreviations

AEs: Adverse events; AML: Angiomyolipoma; DLco: The diffusing capacity of the lung for carbon monoxide; FEV\(_1\): Forced expiratory volume in 1 s; FVC: Forced vital capacity; LAM: Lymphangioleiomyomatosis; mTORC1: Mammalian target of the rapamycin complex 1; SAEs: Serious adverse events; SD: Standard deviation; TSC: Tuberous sclerosis complex

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### Availability of data and materials

Any data generated and/or analysed during the current study are available from the corresponding author on reasonable request.

### Authors’ contributions

HY and JWS take full responsibility for the content of this manuscript, including its data and analysis. JWS made substantial contributions to the conception and design of the study. HY and JWS made substantial contributions to the analysis and interpretation of data. HY and JWS drafted the initial manuscript. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

The study was approved by the Asan Medical Center Institutional Review Board (2016–0480).

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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