The efficacy and safety of low-dose sirolimus for treatment of lymphangioleiomyomatosis

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Abstract

Background: Lymphangioleiomyomatosis (LAM) is a rare disease caused by dysregulated activation of the mammalian target of rapamycin (mTOR). Sirolimus, an inhibitor of mTOR, has been reported to decrease the size of angiomylipomas and stabilize pulmonary function in patients with LAM. However, the optimal dose for the treatment of LAM remains unclear.

Methods: We conducted a retrospective, observational study of 15 patients with LAM who underwent sirolimus therapy for more than 6 months. The efficacy was evaluated by reviewing the patients' clinical courses, pulmonary function and chest radiologic findings before and after the initiation of sirolimus treatment.

Results: All patients had blood trough levels of sirolimus lower than 5 ng/mL. Sirolimus treatment improved the annual rates of change in FVC and FEV1 in the 9 patients who were free from chylous effusion (FVC, −101.0 vs. +190.0 mL/y, p = 0.046 and FEV1, −115.4 vs. +127.8 mL/y, p = 0.015). The remaining 7 patients had chylous effusion at the start of sirolimus treatment; the chylothorax resolved completely within 1−5 months of treatment in 6 of these cases. These results resembled those of previous studies in which blood trough levels of sirolimus ranged from 5 to 15 ng/mL.

Keywords:
Chylous effusion
Lymphangioleiomyomatosis
mTOR inhibitor
Sirolimus

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Deceased. Dr. Masashi Mikami, partly contributed to the acquisition of data.

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1. Introduction

Lymphangioleiomyomatosis (LAM), a rare disease seen primarily in women of childbearing age, is characterized by the proliferation of abnormal smooth muscle-like cells (LAM cells), which lead to cystic destruction of the lungs, chyloous effusions, lymphangioleiomyomas, and, frequently, renal angiomyolipoma (AML) [1,2]. This condition can occur as a sporadic disease (sporadic LAM) or as a pulmonary manifestation of tuberous sclerosis complex (TSC) (TSC-associated LAM) [3-5]. The apparent cause of TSC-associated LAM is mutation of either of the tumor suppressor genes TSC1 and TSC2, whereas sporadic LAM results mainly from mutation of TSC2 [6-8]. Loss of TSC gene function allows constitutive activation of the mammalian target of rapamycin (mTOR) signaling pathway, which regulates multiple cellular functions such as growth, motility, and survival [9].

The mTOR inhibitors such as sirolimus and everolimus block mTOR-mediated activation of downstream kinases and restore homeostasis in cells with defective TSC gene function [9]. Administration of mTOR inhibitors has previously been shown to decrease the size of AML and stabilize lung function in patients with LAM [10,11]. The CAST (Cincinnati Angiomyolipoma Sirolimus Trial) was a phase 1–2 trial comprising 20 patients with TSC or sporadic LAM, and sirolimus reduced the size of renal AML in both groups [10]. In that study, the optimal dose for the reduction of AML was determined by first administering sirolimus at 0.25 mg per square meter of body-surface area to achieve a blood trough level between 1 and 5 ng/mL (1–5 ng/mL). If this did not decrease the size of the target AML by 10% of the baseline value within 2 months, the dose was increased to achieve a trough level of 5–10 ng/mL. Finally, if the lesion did not decrease in size by 10% of the baseline value within 4 months, the dose was increased to achieve a trough level of 10–15 ng/mL, and that dose was continued throughout the next 12 months. Under this regimen, 1 of the 20 patients remained at the initial target trough level of 1–5 ng/mL, whereas the other 19 patients were dosed to reach the highest target level (10–15 ng/mL).

The MILES (Multicenter International LAM Efficacy of Sirolimus) Trial was a double-blind, placebo-controlled trial in which sirolimus was shown to stabilize lung function and improve the quantity of life in patients with LAM [11]. In that trial, sirolimus was administered to maintain blood trough level of 5–15 ng/mL, which was chosen on the basis of results of the CAST. However, it remains unclear whether this is the optimal level for the treatment of LAM, especially as other recent case reports have shown that a lower dose was also effective [12,13]. Therefore, to determine the efficacy and safety of sirolimus at a concentration lower than the currently recommended trough level, we conducted an observational study of Japanese patients with LAM who took sirolimus at doses that maintained blood trough levels lower than the currently recommended target of 5–15 ng/mL.

2. Materials and methods

2.1. Study population

Records from 21 patients with LAM who were treated with sirolimus in the Department of Respiratory Medicine at Juntendo University Hospital between November 2009 and January 2012 were reviewed for this study. We excluded 6 patients for the following reasons: 2 patients discontinued sirolimus treatment within 2 months due to adverse events (drug-induced lung injury and skin rash/chest discomfort, respectively), 1 patient lacked serial data, 2 patients received sirolimus for too short a period to support analysis, and 1 patient underwent lung transplantation. The remaining 15 patients with LAM underwent sirolimus treatment for more than 6 months and had serial data available for retrospective analysis. To determine the efficacy of sirolimus, we retrospectively reviewed the patients’ clinical courses, including adverse events, as documented in their medical records, and compared chest radiologic findings and pulmonary function before and after the initiation of sirolimus treatment. Patients’ data were used under the comprehensive consent from the patients of its use and the approval of IRB (31 July 2007).

All patients were female, and their ages at the initiation of sirolimus therapy ranged from 27 to 56 years (mean, 40 y) (Table 1). Fourteen of the patients had been diagnosed with sporadic LAM and one with TSC-associated LAM. Seven patients had chyloous effusion; all had chylothorax, and 3 of the 7 had chyloous ascites. One patient had renal angiomyolipomas, 2 had pulmonary lymphedema, 2 had abdominal lymphadenopathy, 1 had pelvic lymphadenopathy, and 7 had both abdominal and pelvic lymphadenopathy. The diagnosis of LAM was established by histopathological examination (n=13), by cytological examination of chylous fluid [14] (n=1), or from a combination of characteristic high resolution computed tomography (HRCT) findings and an elevated serum VEGF-D level (n=1). Serum VEGF-D was measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer’s instructions (R&D Systems, Inc., Minneapolis, MN, USA) [15].

Fourteen patients began the regimen with a dose of sirolimus of 1 mg/day. The dose was increased to 2 mg/day to improve the response in 4 cases (JUL46, JUL91, JUL248, and JUL316). Patient JUL97 had been treated for 1 year with everolimus, a similar mTOR inhibitor, at a dose of 1 mg/day before starting treatment with sirolimus. The trough level of sirolimus was measured within 1 month after the initiation...
of treatment or the increase in the dose. Blood sirolimus levels were assayed by Towa Environment Science Co., Ltd., (Osaka, Japan) using the method described by McCormack, et al. [11].

2.2. **The effect of sirolimus on LAM**

Our evaluation of sirolimus in patients with LAM included assessment of the changes in various parameters within the groups of patients with and without chylous effusion. In the 8 LAM patients without chylous effusion (Table 2), we used the Wilcoxon signed-rank test to compare the serial values of pulmonary function, forced vital capacity (FVC), and forced expiratory volume in 1 s (FEV₁) before and after the administration of sirolimus. The statistical analysis was conducted using SPSS version 20. For all statistical analyses, a p value less than 0.05 was considered significant.

For the 7 patients with chylous effusions, we reviewed the size or amount of effusion as assessed by radiologic or ultrasonographic examinations. We defined complete resolution (CR) as the absence of pleural effusion detectable by radiologic examination and a “stabilized” condition as effusion that persisted but in a smaller quantity than present at baseline. For chylous ascites, we defined “stabilized” as ascites that persisted but was no worse than that previously visible and “improved” as a quantity of ascites greater than physiologically normal but less than present at baseline. The patients’ medical records indicated whether the radiologic findings accompanied changes in other parameters related to effusions, such as symptoms (dyspnea, heaviness in the chest, or a feeling of abdominal distention), abdominal circumference, and body weight.

3. **Results**

3.1. **Trough sirolimus levels in the blood**

Of the 15 patients treated with sirolimus who are reviewed here, all had trough blood levels lower than 5 ng/mL (mean, 2.16 ng/mL; range, 0.8–4.3 ng/mL). Accordingly, we arbitrarily designated the treatment regimen “low-dose sirolimus treatment” because the trough levels of all patients were lower than those in previous studies [10,11,16,17].

3.2. **Effect of sirolimus on pulmonary function**

The clinical characteristics of the 8 patients without chylous effusion are shown in Table 2. All of these patients had sporadic LAM, and their ages at the start of sirolimus treatment ranged from 33 to 56 years. The median follow-up time as of August 2012 was 17.5 months (SD, 5.9 months). The most frequent presenting feature was exertional dyspnea, which was noted in 6 of 8 patients (75%). Pneumothorax and retroperitoneal lymphadenopathy were each present in 1 patient. Two patients had pulmonary lymphedema.

Their mean (SE) annual changes in FVC and FEV₁, before sirolimus treatment were −101.0 mL (314.2 mL) and −115.4 mL (86.2 mL), respectively (Table 2 and Fig. 1). The annual change improved after the start of sirolimus treatment for both FVC and FEV₁: FVC, +190.0 mL (246.1 mL), p = 0.046 and FEV₁, +127.8 mL (289.6 mL), p = 0.015. Six of 8 patients had FEV₁ values at or above their baseline values after 1 year, whereas the remaining 2 patients showed slight decreases from baseline in FEV₁ [1.69–1.62 L (JUL123) and 0.85–0.78 L (JUL248)]. These results were similar to those of previous studies in which the blood trough level of sirolimus was maintained at 5–15 ng/mL [11,16,17].

We will briefly describe a clinical course representative of the patients without chylous effusion to depict the typical response to mTOR inhibition. JUL97 presented at 27 years of age with hemoptysis and Polycystic Ovarian Syndrome (PCOS) (Fig. 2). Imaging studies demonstrated lymphatic congestion and edema (predominantly in the right lung). Cystic parenchymal destruction was evident as coalescing, irregular, bizarre shaped, cavity-like, airspaces in the right upper lobe. Everolimus therapy was initiated 5 years later while she was on a waiting list for bilateral lung transplantation. She was receiving supplemental oxygen at 5 L/min for treatment of respiratory failure and her condition was complicated by bloody chylous sputum. Treatment with everolimus for 1 year resolved the bloody chylous sputum, substantially eased the pulmonary lymphedema, and counteracted the airflow limitation. The mTOR inhibitor was then changed from everolimus to sirolimus for financial reasons. Her condition continued to improve, and she no longer requires supplemental oxygen. Later, during the third year of mTOR inhibitor treatment, she developed an Aspergillus infection in her right upper lung lobe, in which severe parenchymal destruction had created a cavity.

**Table 1 – Patients’ characteristics at the initiation of sirolimus therapy.**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>LAM (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age—yr (range)</strong></td>
<td>39.9 ± 8.0 (27–56)</td>
</tr>
<tr>
<td>Sporadic/TSC-associated LAM</td>
<td>14/1</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
</tr>
<tr>
<td>Chylous effusion</td>
<td>7 (46.7)</td>
</tr>
<tr>
<td>Chylothorax only</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Chylothorax with ascites</td>
<td>3 (20.0)</td>
</tr>
<tr>
<td>Pulmonary lymphedema</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Angiomyolipoma</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Abdominal lymphadenopathy</td>
<td>9 (60.0)</td>
</tr>
<tr>
<td>Pelvic lymphadenopathy</td>
<td>8 (53.3)</td>
</tr>
<tr>
<td><em>Home oxygen therapy</em></td>
<td>8 (53.3)</td>
</tr>
<tr>
<td><strong>Diagnostic test</strong></td>
<td></td>
</tr>
<tr>
<td>TBLB</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>VATS</td>
<td>7 (46.7)</td>
</tr>
<tr>
<td>Abdominal lymph node biopsy</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Pelvic tumor resection</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Cytology of chylous fluid</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Clinical diagnosis*</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Serum VEGF-D (pg/mL) (range)</td>
<td>4074 ± 1927 (1346–8281)</td>
</tr>
</tbody>
</table>

+-minus values are means ± SD.
Abbreviations: TBLB, transbronchial lung biopsy; TSC, tuberous sclerosis complex and VATS, video-assisted thoracic surgery.
* Diagnosed on the basis of the combination of characteristic high resolution computed tomography (HRCT) findings and an elevated serum VEGF-D level.

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Table 2 – Patients without chylous effusion.

<table>
<thead>
<tr>
<th>Registry number</th>
<th>Ageb (yr)</th>
<th>Presenting features</th>
<th>Durationc (m)</th>
<th>Trough level</th>
<th>Clinical characteristics</th>
<th>FVCd</th>
<th>FEV1d</th>
<th>Serum VEGF-Dd</th>
<th>Clinical course</th>
</tr>
</thead>
<tbody>
<tr>
<td>JUL46</td>
<td>44</td>
<td>Dyspnea</td>
<td>12</td>
<td>1.2</td>
<td>AML, abdominal lymphadenopathy</td>
<td>2.93</td>
<td>3.05</td>
<td>ND</td>
<td>1250</td>
</tr>
<tr>
<td>JUL97</td>
<td>33</td>
<td>Dyspnea</td>
<td>20</td>
<td>1.2</td>
<td>Pulmonary lymphedema, abdominal and pelvic lymphadenopathy</td>
<td>2.07</td>
<td>2.54</td>
<td>1.56</td>
<td>2.13</td>
</tr>
<tr>
<td>JUL117</td>
<td>55</td>
<td>Dyspnea</td>
<td>13</td>
<td>ND</td>
<td></td>
<td>2.42</td>
<td>2.32</td>
<td>0.47</td>
<td>0.47</td>
</tr>
<tr>
<td>JUL123</td>
<td>37</td>
<td>PTX</td>
<td>23</td>
<td>1.8</td>
<td></td>
<td>2.88</td>
<td>3.00</td>
<td>1.69</td>
<td>1.62</td>
</tr>
<tr>
<td>JUL162</td>
<td>38</td>
<td>Dyspnea</td>
<td>27</td>
<td>2.1</td>
<td>Pulmonary lymphedema</td>
<td>2.7</td>
<td>2.7</td>
<td>1.82</td>
<td>1.99</td>
</tr>
<tr>
<td>JUL197</td>
<td>36</td>
<td>Dyspnea</td>
<td>27</td>
<td>ND</td>
<td></td>
<td>1.05</td>
<td>1.34</td>
<td>0.42</td>
<td>0.44</td>
</tr>
<tr>
<td>JUL210</td>
<td>56</td>
<td>Retroperitoneal lymphadenopathy</td>
<td>15</td>
<td>2.4</td>
<td>Abdominal and pelvic lymphadenopathy</td>
<td>3.34</td>
<td>2.81</td>
<td>1.83</td>
<td>1.96</td>
</tr>
<tr>
<td>JUL248</td>
<td>41</td>
<td>Dyspnea</td>
<td>13</td>
<td>2.4</td>
<td></td>
<td>2.56</td>
<td>2.73</td>
<td>0.85</td>
<td>0.78</td>
</tr>
</tbody>
</table>

All patients were diagnosed with sporadic LAM.
Abbreviations: AML, angiomyolipoma; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ND, not determined and PTX, pneumothorax.

a Registry number: The registry number of each patient with LAM at Juntendo University Hospital. We use this to make it clear when cases have been duplicated in our manuscripts.
b Age at initiation of sirolimus therapy (years).
c The follow-up period after the initiation of sirolimus therapy (months).
d Values of FVC (L), FEV1 (L), and serum VEGF-D (pg/mL) at baseline (pre) and 1 year after the initiation of sirolimus therapy (post).
e See also Fig. 2. JUL97 developed an Aspergillus infection 20 months after the initiation of sirolimus therapy.
3.3. Effect of sirolimus on chylous effusions

Seven patients had chylothorax, which was accompanied in 3 cases by chylous ascites (Table 3). Their median follow-up time as of August 2012 was 12.0 months (SD, 5.5). Four of the patients experienced complete resolution of chylothorax in 1 to 3 months after the initiation of sirolimus treatment. Of the 3 patients with both chylothorax and chylous ascites, 2 experienced complete resolution of the chylothorax and decreased amounts of ascites. Even the remaining patient (JUL79), in whom considerable pleural effusion and ascites persisted, had less fluid accumulation than before sirolimus therapy ("stabilized condition"). This situation may have resulted from her extremely low trough level (0.8 ng/mL).

We will describe a case TSC-associated LAM (JUL316) to illustrate how chylous effusion responded to low-dose sirolimus (Fig. 3). This 47-year-old woman had a moderate amount of right pleural effusion, dilatation of the thoracic duct, and lymphatic involvement in the mediastinum and upper abdomen (Fig. 3A and B). Lymphoscintigraphy revealed obstruction of axial lymphatic flow around the common iliac veins (Fig. 3C). She needed supplemental oxygen therapy to avoid hypoxemia. After taking sirolimus at 1 mg/day for 14 days (trough level, 2.2 ng/mL), she obtained symptomatic relief and amelioration of the lymphatic obstruction, as confirmed by lymphoscintigraphy (Fig. 3D). At her request, her dose of sirolimus was increased to 2 mg/day (trough level, 4.3 ng/mL), and her pleural effusion disappeared completely within 2 months (Fig. 3E). She eventually stopped needing supplemental oxygen.

We observed the effect of discontinuing sirolimus in 1 patient with chylous ascites (JUL137) (Fig. 4). This 43-year-old patient with sporadic LAM had received a peritoneovenous shunt 5 years prior to control intractable chylous ascites [18]. However, the small amount of chylous pleural effusion and moderate amount of chylous ascites that remained expanded her abdominal circumference to ~77–80 cm. Approximately 60 days after starting sirolimus treatment, her abdominal circumference had decreased to 72 cm, the sensation of abdominal distention disappeared, the chylothorax had completely resolved, and her body weight had decreased. However, she began to feel lower abdominal pain, probably because the lack of ascites allowed the tip of the shunt tube to irritate the inner surface of her abdomen. Accordingly, she discontinued the sirolimus therapy. Thereafter, her abdominal circumference gradually increased and returned to the baseline level within 153 days. After removal of the peritoneovenous shunt (data not shown) and reinstatement of sirolimus therapy, her chylous ascites diminished as before.

3.4. The effect of sirolimus on the serum VEGF-D level

Serum VEGF-D levels before and after sirolimus treatment were measured in 14 patients (all except JUL46) (Table 1). Sirolimus treatment decreased the serum VEGF-D level in all but 1 patient (JUL305) (Tables 2 and 3).

3.5. Treatment-related adverse events

The treatment-related adverse events are summarized in Table 4. The most common adverse events related to low-dose sirolimus were stomatitis (9 patients, 60.0%); gastrointestinal episodes (8 patients, 53.3%), including diarrhea (n=6) and stomach discomfort (n=2); and upper or lower respiratory infection (6 patients, 40.0%). Although these were not severe, i.e., usually grade 1 or 2, 1 patient (JUL316) temporarily discontinued sirolimus treatment due to grade 3 stomatitis. Hypercholesterolemia was not observed in any patient. One patient (JUL97) developed Aspergillus infection in her severely damaged lung parenchyma, where a cavity-like area was visible in the right upper lobe.

Fig. 1 – Serial changes in forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV₁) before and after initiation of sirolimus treatment. Day 0 on the horizontal axis indicates the day on which sirolimus therapy was initiated; negative and positive numbers indicate days before and after the initiation of sirolimus administration, respectively.

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4. Discussion

This retrospective study documents the effectiveness of low-dose sirolimus for stabilizing pulmonary function and decreasing chylous effusion in patients with LAM. Our results resemble those of previous studies in which the blood trough level of sirolimus was maintained at 5–15 ng/mL [11,16,17]. Therefore, our data indicate that sirolimus was effective in Japanese patients even at a trough level less than 5 ng/mL. A particularly noteworthy patient was JUL97, a woman with atypical symptoms of severe lymphatic pulmonary edema and bloody chylous sputum who required continuous supplemental oxygen therapy. In contrast, Moua et al. recently described a patient with LAM in whom sirolimus therapy resolved chylous pulmonary congestion and respiratory...

Fig. 2 – Radiologic findings for patient JUL97, whose pulmonary lymphedema resolved after administration of mTOR inhibitors. This patient’s chest radiograph taken at presentation (January 2004) showed ground glass opacity in the right lower lung field (A). Neither pneumothorax nor pleural effusion was found. Lymphoscintigraphy utilizing 99mTc-labeled human serum albumin (HSA) revealed accumulation of radiolabeled HSA in the right lower lung field, as well as in the retroperitoneal and pelvic lymphangioliomyomas, 60 min after subcutaneous injection of 99mTc-labeled HAS into the dorsal foot skin, indicating the presence of pulmonary lymphedema (B). Note the double thoracic ducts. Computed tomography (CT) images of the chest showed severe cystic destruction with irregular and bizarre shapes, especially in the right upper, right lower, and left lower lobes, as well as ground glass opacity and thickening of the interlobular septa, indicating pulmonary lymphedema (C, April 2009). Administration of everolimus at 0.5 mg/day began in April 2009, and the dose was increased to 1 mg/day from August 2009 through April 2010. CT images of the chest taken in April 2010 showed lessening of the pulmonary lymphedema (D). The mTOR inhibitor was then changed to sirolimus at 1 mg/day, and CT images of the chest in January 2011 showed almost complete resolution of the pulmonary lymphedema (E).
toxicities. The incidence was similar to those previously reported despite the low-dose regimen [10,11]. There were 2 exceptions. One patient with possible sirolimus-related lung injury (2 mg/day; trough level not measured), which has never previously been reported in studies of patients with LAM, was excluded from this analysis. At baseline, this patient as receiving continuous supplemental oxygen due to respiratory failure; however, she was hospitalized and cured without specific treatment after discontinuation of sirolimus. The second was a patient with moderately limited airflow at baseline who developed mild chest tightness with slightly increased parenchymal opacity on chest radiographs after sirolimus treatment (1 mg/day; trough level, 3.7 ng/mL). These symptoms and findings resolved promptly after the discontinuation of sirolimus. Aspergillus infection developed in 1 patient (JUL97), indicating that particular caution is needed when prescribing mTOR inhibitors for any patient with LAM with an area of pulmonary airspace destruction. Meanwhile, hypercholesterolemia, one of the most common adverse events in earlier studies of LAM patients [10,11], was not observed in the present study. A subgroup analysis of the MILES trial recently showed that the types of adverse events differed between Japanese and American patients [20]. Accordingly, there may be racial differences in susceptibility to specific adverse events.

Our study had several limitations. First, the small number of patients included in this observational study could have biased the results. However, considering the rarity of LAM, our analysis of 15 patients is likely to be one of the larger such studies and thus warrant attention. Second, because our retrospective study was not controlled, it is possible that the pleural effusions might have resolved spontaneously. This possibility was raised in the previous study [16] but was deniable because we verified

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**Table 3 – Patients with chylothorax.**

<table>
<thead>
<tr>
<th>Registry number</th>
<th>Age (yr)</th>
<th>Site</th>
<th>Duration (months)</th>
<th>Trough level</th>
<th>Clinical characteristics</th>
<th>Response of chylothorax (time)</th>
<th>Response of ascites</th>
<th>Serum VEGF-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>JUL235</td>
<td>39</td>
<td>R</td>
<td>19</td>
<td>2.0</td>
<td>Alveolar hemorrhage, abdominal lymphadenopathy</td>
<td>CR (1 month)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JUL240</td>
<td>28</td>
<td>R</td>
<td>7</td>
<td>3.3</td>
<td>Abdominal and pelvic lymphadenopathy</td>
<td>CR (1 months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JUL305</td>
<td>27</td>
<td>R</td>
<td>9</td>
<td>1.7</td>
<td>Abdominal and pelvic lymphadenopathy</td>
<td>CR (3 months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JUL316</td>
<td>47</td>
<td>R</td>
<td>12</td>
<td>4.3</td>
<td>Abdominal and pelvic lymphadenopathy</td>
<td>CR (2 months)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Chylothorax with ascites**

<table>
<thead>
<tr>
<th>Registry number</th>
<th>Age (yr)</th>
<th>Site</th>
<th>Duration (months)</th>
<th>Trough level</th>
<th>Clinical characteristics</th>
<th>Response of ascites</th>
<th>Serum VEGF-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>JUL79</td>
<td>38</td>
<td>L</td>
<td>12</td>
<td>0.8</td>
<td>Pelvic lymphadenopathy</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>JUL91</td>
<td>36</td>
<td>B</td>
<td>19</td>
<td>2.7</td>
<td>Chylous vaginal discharge, abdominal and pelvic lymphadenopathy</td>
<td>CR (5 months)</td>
<td></td>
</tr>
<tr>
<td>JUL137</td>
<td>43</td>
<td>R</td>
<td>21</td>
<td>2.2</td>
<td>Peritoneovenous shunt had been placed. Abdominal and pelvic lymphadenopathy</td>
<td>CR (2 months)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response and SD, stable disease.

* JUL316 had TSC-associated LAM (All other patients had sporadic LAM.).

* Site of chylothorax: B, bilateral; L, left and R, right.

* Time elapsed before response (months).
that long-term GnRH therapy and a low-fat diet did not resolve the chylous effusions in our patients before initiating sirolimus treatment.

In conclusion, careful review of Japanese patients with LAM who were treated with low doses of sirolimus provided clear evidence of improved or stabilized pulmonary function and decreased chylous effusions. Even at a blood trough level of less than 5 ng/mL, sirolimus appears to be clinically beneficial in terms of effectiveness, cost, and safety. The results of our retrospective study warrant a prospective study to compare the effects of low (< 5 ng/mL) and conventional (5–15 ng/mL) doses of sirolimus on the clinical course of LAM.

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