Everolimus treatment of abdominal lymphangioleiomyoma in five women with sporadic lymphangioleiomyomatosis

Abstract

Objective: Lymphangioleiomyomatosis (LAM) is a rare systemic disease of young women arising from mutations in the tuberous sclerosis complex (TSC) genes, TSC1 or TSC2. This disrupts the mammalian target of rapamycin (mTOR) pathway, affecting cellular proliferation and growth. mTOR inhibitors are a promising novel therapy in LAM. The mTOR inhibitor sirolimus is reported to produce resolution of lymphatic abnormalities in LAM, but the efficacy of the mTOR inhibitor everolimus has not been assessed. We aimed to examine the efficacy of everolimus on lymphatic abnormalities in LAM.

Design, setting and participants: Open-label treatment of five patients with sporadic LAM (sLAM) and abdominopelvic and lung involvement at the outpatient LAM clinic of a tertiary city teaching hospital. Clinical data were collected during treatment of the women and included regular clinical reviews, everolimus levels, lung function and computed tomography assessment before and after 6 months of everolimus treatment.

Main outcome measures: Symptoms and level of resolution of lymphangioleiomyomas.

Results: All five women experienced significant shrinkage or complete resolution of the lymphangioleiomyomas during treatment. In one woman, cessation of everolimus resulted in recurrence of symptoms. Adverse events were compatible with the known side-effect profile of everolimus, but overall the drug was well tolerated.

Conclusions: This is the first report to suggest that everolimus has efficacy in the treatment of lymphangioleiomyoma and chylous ascites in sLAM.

Methods

Patients

Five women (mean age, 35.2 years) with clinically significant abdominal lymphangioleiomyoma, with or without chylous ascites, were treated with everolimus at St Vincent's Hospital, Sydney, where a LAM clinic is established. The two women treated at the LAM clinic were prospectively studied according to a standardised protocol, while the three women seen as private patients are reported retrospectively. All five women had a histopathologically confirmed diagnosis of sLAM, according to European Respiratory Society guideline criteria. All women gave written, informed consent to publication of this case series. Treatment of the women at the LAM clinic was approved by the St Vincent's Hospital Drug Committee, and the everolimus therapy was funded by the hospital at an estimated cost of about $10 000 per patient per year.

Clinical features of the participating women are shown in Box 1. All women
had lung involvement with varying severity. Three of the women had been treated for abdominal LAM before everolimus therapy, without success.

**Everolimus treatment**

Patients were treated with twice daily everolimus at a starting dose of 0.5 mg twice daily or 0.75 mg twice daily. Serum everolimus levels were monitored and the dose was titrated to maintain target serum concentrations of 2–4 μg/L, which is the low end of the therapeutic range used for lung transplantation (3–8 μg/L). Data collected included lung function at baseline and at 6 months, serial abdominopelvic imaging and regular blood monitoring, including liver function tests and blood lipid levels. Patients were seen initially after the first 2 weeks, then at 1 month, 3 months and 6 months unless side effects determined more frequent review. At each review, patients were monitored for adverse effects by clinical examination and blood tests, including everolimus levels. Lung function testing was repeated at 2 months and 6 months, and computed tomography scans were repeated at 6 months. All patients currently continue with everolimus therapy.

**Results**

**Abdominal lymphangioleiomyomas and chylous ascites**

All five patients had significant abdominal lymphangioleiomyomas at baseline, the largest of these measuring 17.5 cm at its maximum dimension (Box 1 and Box 2). Two patients had chylous ascites at baseline. Six months after initiation of everolimus, four of the five participants had experienced significant shrinkage or complete resolution of their lymphangioleiomyomas, and of the chylous ascites (where applicable). One woman experienced clinical resolution of her abdominal pain and distress but did not have confirmatory follow-up imaging due to financial constraints. In one woman, temporary cessation of everolimus resulted in recurrence of abdominal distension, requiring reinitiation of therapy.

**Lung function**

Lung function was abnormal in all five patients at presentation. There was no significant change in any lung function parameter over the treatment period, whereas a decline would possibly have been expected. However, no patient had severe lung involvement, one had a chylothorax at presentation and the overall number of patients was very small. Interpretation of these results is difficult because of the small number of patients. In the patient with chylothorax, complete resolution occurred.

**Adverse events**

The commonest adverse events were buccal ulcers and respiratory tract infections, which are consistent with the known side effects of everolimus. The most severe adverse event that occurred during treatment was in Patient 1, who developed appendicitis, which required appendicectomy. All women continued to menstruate throughout treatment, but Patient 5 had a new onset of heavy vaginal bleeding, which was investigated urgently in view of the fact that she was perimenopausal and everolimus treatment has been previously described as being associated with amenorrhoea. The patient was diagnosed with Stage 1 endometrial carcinoma, and was successfully treated with hysterectomy. Adverse events experienced by the participants are summarised in Box 1.

**Discussion**

Although LAM frequently presents with respiratory symptoms, abdominal involvement occurs in up to 70% of cases, with abdominal lymphangioleiomyomas in 16% of cases. Women may present with abdominal pain and swelling, and refractory chylous ascites, or with non-specific signs such as infertility or perimenstrual abdominal discomfort. Treatment is generally unsatisfactory, with medical therapies ineffective, and repeated abdominocentesis resulting in fluid reaccumulation, protein loss and potential infection.

The use of mTOR therapy in LAM is a targeted approach to an abnor-

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**1 Characteristics of patients with sporadic lymphangioleiomyomatosis treated with everolimus**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25</td>
<td>36</td>
<td>29</td>
<td>33</td>
<td>53</td>
</tr>
<tr>
<td>Smoking history</td>
<td>Never smoked</td>
<td>10 pack-years, quit at 36 years</td>
<td>Never smoked</td>
<td>Never smoked</td>
<td>“Social” smoker (&lt; 1 pack-year)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Uterine fibroids, endometrial polyp, bilateral breast fibroadenomata, phyllodes tumour (right breast)</td>
<td>Childhood asthma</td>
<td>Polycystic ovary syndrome, depression</td>
<td>None</td>
<td>Childhood asthma, uterine fibroids</td>
</tr>
<tr>
<td>Presentation</td>
<td>Recurrent bilateral pneumothoraces</td>
<td>Abdominal pain and distension</td>
<td>Incidental abdominal mass</td>
<td>Infertility, abdominal distension</td>
<td>Recurrent bilateral pneumothoraces</td>
</tr>
<tr>
<td>Lymphangioleiomyoma size at presentation*</td>
<td>8.3 cm × 4.3 cm × 17.5 cm</td>
<td>3 cm × 1 cm (coronal view)</td>
<td>9 cm × 3.5 cm (sagittal view)</td>
<td>5.1 cm × 2.3 cm (axial view)</td>
<td>3.1 cm × 10 cm (axial view)</td>
</tr>
<tr>
<td>Lymphangioleiomyoma size after 6 months’ everolimus treatment*</td>
<td>Undetectable</td>
<td>Virtually undetectable</td>
<td>Clinical resolution</td>
<td>3.7 cm × 1.8 cm (axial view)</td>
<td>Undetectable</td>
</tr>
<tr>
<td>Treatment of abdominal LAM prior to everolimus</td>
<td>None</td>
<td>Radiotherapy, doxycycline</td>
<td>Surgical excision, abdomino-centesis</td>
<td>Doxycycline</td>
<td>None</td>
</tr>
<tr>
<td>Adverse events while being treated</td>
<td>URTI, influenza A, ear pain, acute appendicitis</td>
<td>Nausea, upper respiratory tract infection</td>
<td>Acne exacerbation</td>
<td>Buccal ulcer, sciatica, transaminitis, lymphopenia, myalgia</td>
<td>Buccal ulcers, diarrhoea, vaginal bleeding diagnosed as endometrial carcinoma</td>
</tr>
</tbody>
</table>

CT = computed tomography. LAM = lymphangioleiomyomatosis. URTI = upper respiratory tract infection. * Measured using CT.

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Everolimus is a derivative of sirolimus and has a very similar side-effect profile. It has a shorter elimination half-life (about 30 hours) and greater relative bioavailability, compared with sirolimus. We used a lower dose of everolimus than the dose of sirolimus that was used in the MILES trial. The everolimus dose we used was consistent with the lower range of doses used in lung transplantation in our centre, with the aim of producing fewer side effects. Overall, everolimus was well tolerated and side effects, although significant, were within its described profile.

In summary, all women with sLAM showed a good response to treatment, with disappearance or shrinkage of abdominal lymphangioleiomyomas in four of five of cases, and clinical resolution of the lymphangioleiomyoma in the fifth. Abdominal symptoms resolved. Cessation of the therapy in one patient resulted in recurrence of ascites, and reinstitution of treatment resulted in resolution again. This is similar to the MILES trial, in which continued treatment was required.

We suggest that everolimus treatment may be an effective long-term therapy for lymphangioleiomyomas and chylous ascites, which requires further evaluation in an appropriately designed controlled trial.

Competing interests: No relevant disclosures.

Received 22 Oct 2012, accepted 13 Mar 2013.