Low-dose rapamycin reduces kidney volume angiomyolipomas and prevents the loss of renal function in a patient with tuberous sclerosis complex

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Abstract
Tuberous sclerosis complex (TSC) is caused by constitutively activated mammalian target of rapamycin (mTOR) resulting in non-malignant tumours of several organs including renal angiomyolipomas (AMLs). AMLs may originate renal failure, hypertension and spontaneous life-threatening bleeding. Recent reports suggest a possible beneficial role of the mTOR inhibitor rapamycin for TSC. However, safety and efficiency of rapamycin in TSC patients as an anti-proliferative agent are still undefined. A 40-year-old man with sporadic TSC and a history of spontaneous bleeding from his left kidney AMLs received low-dose rapamycin for 12 months, and this was associated with a reduction in bilateral kidney AML volume, stabilization and even improvement of renal function. There was also a reduction of facial angiofibromas, improvement of blood pressure control and absence of AML bleeding over this time period. Brain lesion images remained stable, and no significant rapamycin-associated side effects were noted. To the best of our knowledge, this is the first report of a case of reduction in renal AML volume together with preservation of renal function in a patient with TSC receiving low-dose rapamycin. These data suggest that it could be the result of the anti-angiogenic, anti-fibrotic and anti-proliferative effects of rapamycin.

Keywords: angiomyolipomas; mTOR; rapamycin; renal function; tuberous sclerosis

Introduction
Tuberous sclerosis complex (TSC), a rare autosomal dominant disorder with variable penetrance, affects ~1 in 10 000 people [1–6]. TSC is caused by mutations of TSC1 or TSC2 genes. Products of these genes, hamartin and tuberin, create a complex that inhibits mTOR, a key protein engaged in regulation of the cell cycle. Mutations of TSC genes lead to constitutive activation of mTOR resulting in uncontrolled proliferation, differentiation and migration of cells. As a consequence, malformations of many organs arise. Angiomyolipomas (AMLs) are benign but progressive tumours consisting of smooth muscle, fat and vascular elements, commonly associated with the TSC. Kidney enlargement resulting from the expansion of AMLs in patients with TSC is associated with a reduction in renal function and elevation of blood pressure. Higher rates of kidney AML enlargement are associated with a more rapid decrease in renal function. In addition, TSC may become symptomatic with acute complications such as spontaneous AML haemorrhage (intratumoral or retroperitoneal) [6–8]. TSC subjects with more episodes of gross haematuria have a larger renal AML size and higher serum creatinine levels than those with fewer episodes. Currently, apart from invasive interventions such as embolization or removal of the entire kidney, no medical treatment for TSC patients with severe bleeding from AMLs is available. However, the observation that AML size correlates with the risk of haemorrhage suggests that pharmacotherapy that reduces renal AML size may reduce the risk of bleeding [6].

Rapamycin, an inhibitor of mTOR, has proven highly effective in reducing renal AMLs in animal models of TS [2,3]. In addition, using rapamycin to treat transplant recipients suffering from TSC has resulted in a significant reduction in renal AML volume [9–11]. However, the effect of low-dose rapamycin in renal AML volume and renal function of non-transplanted patients with TSC has not been established.

Case report
A 40-year-old man was first diagnosed with sporadic TSC at age 10 months after presenting with facial angiofibromas and epilepsy. He remained under regular neurologic
control, taking anti-convulsive drugs. No seizures occurred for years, and anti-convulsive drugs were discontinued at age 25 years. He was a graduate in geography and history. The patient presented in October 2006 with acute left flank pain, increased abdominal distension, fever and macroscopic haematuria. There were signs and symptoms of internal bleeding (hypotension, tachycardia and acute anaemia). At admission, the serum creatinine was 1.60 mg/dL (141.44 μmol/L). Ultrasonography and computerized tomography (CT) of the abdomen showed both kidneys with multiple AMLs and some cysts of different sizes scattered throughout the parenchyma. The bleeding source was from an AML lesion of the upper pole of the left kidney that showed evidence of a large intrarenal haematoma (Figure 1A). The liver presented with some AMLs scattered throughout the parenchyma. Renal function deteriorated, and serum creatinine reached 1.90 mg/dL (167.96 μmol/L), and poor blood pressure control. Then, hypertension was treated with telmisartan 80 mg daily, hydrochlorothiazide 12.5 mg daily and atenolol 100 mg daily. CT of the brain showed calcification of the right hemisphere of the cerebellum and several subependymal calcified nodules adjacent to the inferior aspect of both lateral ventricles and around both foramina of Monro.

Because human trials of TSC have shown an effect of rapamycin on renal AMLs, on February 2009, our patient was administered with rapamycin (1 mg/day) orally for 12 months, aiming for trough levels of 1–4 ng/mL. Informed consent for off-label therapy (compassionate use) with rapamycin during this period was obtained. The treatment was well tolerated. Renal function, proteinuria, lipid profile, blood rapamycin levels and total kidney volume measured by magnetic resonance imaging (MRI) were monitored throughout the treatment phase. Drug levels were measured by chemiluminescent automated assay (CMIA) ARCHITECT® Sirolimus assay (Abbott Diagnostics). In this patient, the volumes of both kidneys were assessed by MRI at Month 0 and 12, and were determined using a manual segmentation protocol. On each MRI section, the outlines of the kidneys were manually drawn, and the renal volumes were calculated by multiplying all outline areas by the section thickness and summing the volume of each section. MRI, 12 months after the start of rapamycin, demonstrated a reduction of total kidney volume, from 1480 to 1224 mL (256 mL, 17%); left, from 1081 to 912 mL (16%); right, from 399 to 312 mL (22%) (Figures 2 and 3). At this time, serum creatinine was 1.58 mg/dL (139.67 μmol/L), GFR (MDRD) was 52 mL/min/1.73 m² and urine protein did not change (Table 1). In addition, the patient noticed that his facial angiofibromas had improved (the lesions were smaller and paler). MRI of the brain did not change. The patient had not experienced significant side effects related to rapamycin: haematological parameters and liver function tests were normal. Serum total cholesterol and triglycerides levels remained controlled with treatment with simvastatin 20 mg daily, and atenolol dose was reduced to 50 mg daily. His treatment with low-dose rapamycin is continuing.
Discussion

Our results demonstrate that rapamycin 1 mg/day given for 12 months resulted in a reduction of total kidney volume of 256 mL (17%) in this patient with TSC. In addition, renal function stabilized and even improved over this time period, GFR (MDRD) previously 42 mL/min/1.73 m², and after 52 mL/min/1.73 m². One possible explanation for this finding is that less AMLs and cystic compression of remaining renal parenchyma and vasculature with rapamycin treatment led to increased renal function. By inhibiting vascular remodelling, angiogenesis and fibrogenesis, rapamycin may attenuate nephroangiosclerosis, AML and cyst growth, and interstitial fibrosis. Thus, rapamycin may benefit TSC at multiple levels.

Several recent case reports and clinical trial studies in TSC patients with renal AMLs confirmed that AMLs regressed in response to rapamycin therapy [4–8,12]. However, after discontinuation of rapamycin, variable regrowth of AMLs was observed. In one case, there was a significant decrease in AML volume (83% at 6 months), but regrowth was noted 8 months after rapamycin discontinuation [4]. In another case, in which rapamycin induced a reduction in the volume of AMLs during 2 years of treatment, AMLs remained stable after 6 months of rapamycin withdrawal [5]. In a clinical trial study, the tumour volume decreased
Fig. 3. Axial MRI of a TSC patient with renal AMLs before (A and C) and after (B and D) a 12-month treatment with low-dose rapamycin. Volumetry showed a decrease of total kidney volume from 1480 to 1224 mL (17%).

Table 1. Laboratory values of a TSC patient treated for 12 months with rapamycin

<table>
<thead>
<tr>
<th>Date</th>
<th>Cr mg/dL (μmol/L)</th>
<th>GFR (MDRD) mL/min/1.73 m²</th>
<th>Prot/Cr (urine)</th>
<th>Rapamycin dose mg/day</th>
<th>Rapamycin levels ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 February 2008</td>
<td>1.84 (162.65)</td>
<td>40</td>
<td>0.09</td>
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</tr>
<tr>
<td>18 July 2008</td>
<td>1.74 (153.81)</td>
<td>42</td>
<td>0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 February 2009</td>
<td>1.59 (140.55)</td>
<td>47</td>
<td>0.08</td>
<td>1</td>
<td>2.4</td>
</tr>
<tr>
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<td>1.79 (158.23)</td>
<td>41</td>
<td>0.16</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
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<td>1.67 (147.62)</td>
<td>44</td>
<td>0.14</td>
<td>1</td>
<td>4.5</td>
</tr>
<tr>
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</tr>
<tr>
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<td>0.18</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>8 March 2010</td>
<td>1.58 (139.67)</td>
<td>52</td>
<td>0.24</td>
<td>1</td>
<td>2.60</td>
</tr>
</tbody>
</table>
Rapamycin in tuberous sclerosis

by 53.2% ± 26.6% of the baseline value after 12 months of treatment [6]. Subsequent tumour regrowth occurred in a certain number of patients who reached the 24-month evaluation point. In another study, the AMLs showed a reduction in the longest diameters of 26.1% ± 10.3% at 12 months [7]. In all these studies, renal function did not change or was not communicated. Therefore, it is unclear whether the reduction in tumour size translates to a reduced risk of complications from AMLs [8].

On the other hand, all these studies used a relatively high dose of rapamycin, as compared with our patient, and serious adverse events were present in some patients [6]. Moreover, the blood levels of rapamycin achieved in these patients were similar to those used in transplantation medicine [4–11]. Renal AMLs in our patient responded at a low dose of rapamycin, where side effects are likely to be fewer. Improved blood pressure control, increased GFR (MDRD) of 10 mL/min/1.73 m² and the absence of proteinuria with no alteration in the lipid profile were likewise observed. To our knowledge, this is the first case of a reduction in renal AML volume associated with preservation of renal function in a TSC patient with a mild renal failure receiving a low dose of rapamycin.

How this translates to reduced risk of haemorrhagic complications from renal AMLs is unclear, as are the annual growth rates of AMLs in untreated controls [6]. Currently, there is no effective treatment available to retard AML growth and to prevent progression to renal failure in patients with TSC. Moreover, the therapeutic options to control severe bleeding from the AMLs are limited. We show that low-dose rapamycin reduced the renal AML volume and delayed the loss of renal function in our patient. The fact that there were no further episodes of bleeding during treatment reinforces the concept that rapamycin affects AML growth and its consequences. This fact could also partly account for the observed efficacy in reduction of renal AML volume. An anti-angiogenic (affecting vascular endothelial growth factor levels), anti-fibrotic and anti-proliferative role has been suggested [8], although its ability to reduce the risk of haemorrhagic complications from renal AMLs has not been established. These findings are preliminary and do not in themselves prove the efficacy of rapamycin for the treatment of TSC-associated AML bleeding.

In conclusion, we believe that the therapeutic effect of rapamycin in TSC results from a direct reduction of AMLs and cystic volume. Thus, treatment with a low dose of rapamycin for 12 months resulted in a decrease in renal AML volume with preservation and even improvement of renal function in this TSC patient with a mild renal failure.

Rapamycin could prove useful for retarding progressive renal failure in patients with TSC. Moreover, rapamycin may be considered as an alternative to arterial embolization or surgery for symptomatic AMLs, or as an adjuvant treatment. Rapamycin may also serve as an initial treatment to facilitate surgery for unresectable AMLs. These results, although encouraging, require confirmation and further elucidation by subsequent prospective trials.

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Conflict of interest statement. None declared.

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