

Everolimus in the treatment of giant renal angiomyolipoma associated with tuberous sclerosis

Uso de everolimus no tratamento de angiomiolipomas renais associados à esclerose tuberosa

Miguel Oliveira¹, Marta Sofia Costa¹, Tiago Barra¹, Andreia Silva¹, Tânia Sousa¹, Joana Rodrigues², Filipa Costa², Sérgio Lemos¹

¹ Nephrology and Dialysis Unit, Centro Hospitalar Tondela-Viseu, Portugal

² Department of Imagiology, Centro Hospitalar Tondela-Viseu, Portugal.

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ABSTRACT

Tuberous sclerosis complex is an autosomal dominant disorder characterized by the development of multiple tumours in distinct organs, although the ones most frequently affected are the skin, central nervous system, kidney, lung and liver. The kidney is the third most frequently affected organ, and angiomyolipomas are the most common lesions. Two-thirds of patients have sporadic mutations of the genes responsible for the disease, called tuberous sclerosis complex 1 and 2, encoding hamartin and tuberin, respectively. Hamartin and tuberin are tumoural suppressor proteins that are engaged in the control of cell proliferation and differentiation. When the tuberous sclerosis complex 1-2 suffers mutation, the mammalian target of rapamycin complex 1 pathway is constitutively activated, leading to neoplastic growth. Everolimus is a drug that inhibits mammalian target of rapamycin pathway and it is being used successfully in the treatment of renal angiomyolipomas associated with tuberous sclerosis complex. The authors report a case of a 34-year-old woman with tuberous sclerosis and giant renal angiomyolipoma, who received everolimus 10 mg daily for 6 months, but this was not associated with a reduction in the angiomyolipoma volume. This case describes the use of a systemic therapy in a rare genetic disorder. Although the treatment with everolimus did not reduce the patient's renal angiomyolipoma volume and, thus, was apparently ineffective, no new lesions, bleeding episodes or deterioration of the kidney function were observed, suggesting that everolimus may have prevented disease progression.

Key-Words: Everolimus; renal angiomyolipoma; tuberous sclerosis.

RESUMO

A esclerose tuberosa é um distúrbio genético de transmissão autossômica dominante caracterizado pelo desenvolvimento de múltiplos tumores em diversas localizações, sendo a pele, o sistema nervoso central, rim, pulmão e fígado os órgãos mais afetados. O rim é o terceiro órgão mais afetado, e o angiomiolipoma

é a lesão mais comum. Cerca de dois terços dos doentes apresentam mutações esporádicas dos genes responsáveis pela doença, designados *Tuberous sclerosis complex 1* e *2*, que codificam as proteínas hamartina e tuberina, respetivamente. São ambas proteínas supressoras tumorais, estando envolvidas no controlo da proliferação e diferenciação celulares. Quando mutadas, ocorre sobre-ativação da via *mammalian target of rapamycin complex 1*, levando ao desenvolvimento tumoral. O everolimus é um fármaco inibidor da via *mammalian target of rapamycin complex 1* e, desta forma, tem sido usado com sucesso no tratamento dos angiomiolipomas renais dos doentes com esclerose tuberosa. Os autores relatam o caso clínico de uma doente com 34 anos com esclerose tuberosa e com angiomiolipoma renal gigante, tratada com everolimus 10 mg/dia durante 6 meses, sem contudo haver redução do volume do tumor. Este caso descreve a utilização de uma terapêutica sistémica num distúrbio genético raro: apesar de o everolimus ter sido ineficaz na redução do volume do angiomiolipoma renal da doente durante o período de tratamento, não houve registo de desenvolvimento de novas lesões, episódios de hemorragia ou deterioração da função renal, sugerindo que o everolimus pode ter prevenido a progressão da doença.

Palavras-Chave: Angiomiolipoma renal; esclerose tuberosa; everolimus.

■ INTRODUCTION

Tuberous sclerosis complex (TSC) is a genetic disorder characterized by the growth of benign lesions (hamartomas) in multiple organs¹. It was described for the first time, in 1862, by von Recklinghausen and, according to the most recent studies, tuberous sclerosis affects 1 in 6000-10000 live births^{1,2}.

It is an autosomal dominant disturbance³, and two thirds of affected patients have sporadic mutations¹. The responsible genes are designed TSC1 and TSC2, located in chromosomes 9 and 16, respectively⁴. TSC1 and TSC2 genes encode hamartin and tuberlin¹. The complex TSC1-TSC2 plays an important role in cell proliferation and differentiation, by inhibiting various oncogenes; so, complex TSC1-TSC2 mutations cause the development of multiple hamartomas^{5,6}. Under physiological conditions, complex TSC1-TSC2 inhibits mammalian target of rapamycin complex 1 (mTORC1) signalling pathway, which is engaged in cell cycle regulation^{1,5-8}. When the complex TSC1-TSC2 suffers mutation, mTORC1 pathway undergoes constitutive activation, resulting in uncontrolled cell proliferation, differentiation and migration, and leading to tumoural growth⁷.

Clinical manifestations of TSC include hamartomas in the skin, central nervous system, kidney, lung and heart, although tumours can arise in virtually any organ or tissue^{1,2}.

The diagnosis can be established using genetic or clinical diagnostic criteria². The identification of a either a TSC1 or pathogenic mutation (defined as a mutation that clearly prevents protein synthesis or inactivates the function of TSC1 or TSC2 proteins – nonsense or missense mutations, frameshift mutation, large genomic deletions) is sufficient to make a definitive diagnosis of TSC². However, in 10-25 % of patients with TSC there is no mutation identified by conventional genetic testing². Clinical diagnostic criteria include 11 major features and six minor features (Table I). A definitive diagnosis is made when

Table I

Clinical diagnostic criteria for tuberous sclerosis complex

Clinical diagnostic criteria	
Major features	Minor features
Hypomelanotic macules (≥ 3, at least 5mm diameter)	“Confetti” skin lesions
Angiofibromas (≥ 3) or fibrous cephalic plaque	Dental enamel pits (≥ 3)
Ungual fibromas (≥ 2)	Intraoral fibromas (≥ 2)
Shagreen patch	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts
Cortical dysplasias	Non-renal hamartomas
Subependymal nodules	
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
Lymphangiioleiomyomatosis	
Angiomyolipomas (≥ 2)	

Adapted from Reference #2

two major features, or one major and two minor features can be shown².

The kidney is the third most affected organ, after the skin and central nervous system, and renal lesions vary from angiomyolipomas, cysts and malignant tumours³. Angiomyolipoma is the most common lesion, occurring in 75-80% of patients^{3,9}, and it is the main cause of death and morbidity in TSC⁹.

Angiomyolipomas are non-encapsulated benign bilateral tumours, composed of smooth muscular tissue, adipose tissue and blood vessels^{3,4,8-11}. Blood vessels are abnormal and dysmorphic and have micro or macro aneurysms³; therefore, angiomyolipomas can suffer rupture leading to potentially fatal haemorrhage^{3,4,9}. The risk of haemorrhage depends on volume of angiomyolipoma (> 4 cm), growth rhythm of tumour, and size of aneurysms (> 0.5 cm)⁹. Angiomyolipomas also distort and compress renal parenchyma and are an important cause of chronic kidney disease in these patients, sometimes requiring renal replacement therapy^{3,9}.

There are several therapeutic options for angiomyolipoma treatment, and these include partial or total nephrectomy, enucleation, arterial embolization³, and radiofrequency ablation (RFA)¹²⁻¹⁴; however, whichever the treatment used it should preserve the largest possible volume of renal parenchyma, because these patients tend to develop new lesions and angiomyolipoma usually recur after treatment⁷.

Everolimus is an mTORC1 inhibitor, reducing angiomyolipomas volume in an efficient and safe way; therefore, everolimus is a potential treatment for TSC-associated angiomyolipoma⁷.

■ CASE REPORT

A 34-year-old woman was first diagnosed with sporadic TSC at age 12 months, after investigation due to facial cutaneous angiofibromas and seizures secondary to subependymal nodules. She also has giant renal bilateral angiomyolipoma (all manifestations are listed in Table II). In 2011 she was submitted to total nephrectomy of the left kidney due to uncontrolled haemorrhage; and arterial embolization was

Table II

Patients clinical manifestations of tuberous sclerosis

CNS*	Cortical tubers; subependymal nodules
Skin	Multiple facial angiofibromas
Kidney	Bilateral angiomyolipomas (previous left kidney total nephrectomy secondary to angiomyolipoma rupture with uncontrolled bleeding)
Lung	Lymphangioleiomyomatosis

*Central nervous system

required twice before due to right angiomyolipoma rupture with subsequent haemorrhage.

She was taking anti-convulsive drugs (sodium valproate 500 mg daily) and anti-psychotic drugs (quetiapine 100 mg daily) due to panic disorder; she had been under exogenous hormonal therapy with etonogestrel implant that was removed in 2013.

The patient remains under regular urological and neurological control, and has not experienced new convulsive episodes for many years. A magnetic resonance imaging (MRI) of the brain made, in 2013, showed multiple cortical tubers and subependymal nodules that were unchanged in comparison with previous scans; subependymal giant cell astrocytomas were not identified.

The patient was referred to the nephrology clinic for the first time in February 2014 due to chronic kidney disease stage 3 b, with an eGFR 34 mL/min/1.73 m² (estimated by the CKD-EPI equation), in the context of a right remnant kidney with angiomyolipoma. Her blood pressure was normal.

Ultrasonography of the right kidney showed voluminous lesion compatible with a giant angiomyolipoma. In June 2014 she underwent a thoracic and abdominal computerized tomography (CT) in order to characterize renal lesion and exclude cardiac and lung tumours; she refused abdominal MRI due to her panic attack disorder. The CT scan showed numerous thin-walled cysts scattered throughout the lungs, a characteristic finding of lymphangioleiomyomatosis, and a giant renal angiomyolipoma with 19x10.2x11.4 cm occupying the whole right renal parenchyma (Figs.1 and 2); there was no evidence of cardiac tumours. She was observed in the pneumological

clinic for the first time in July 2014: she had no symptoms of respiratory disease and pulmonary function tests were normal.

According to her urologist's opinion, her renal angiomyolipoma had a very high risk of rupture, and could not be treated by another selective arterial embolization because of the loss of the remaining renal tissue.

So, considering the patient's high risk of angiomyolipoma rupture with life-threatening haemorrhage, we proposed and discussed with the patient

Figure 1

Thoracoabdominal CT scan (sagittal view) showing a giant angiomyolipoma before the beginning of treatment with everolimus (June 2014).

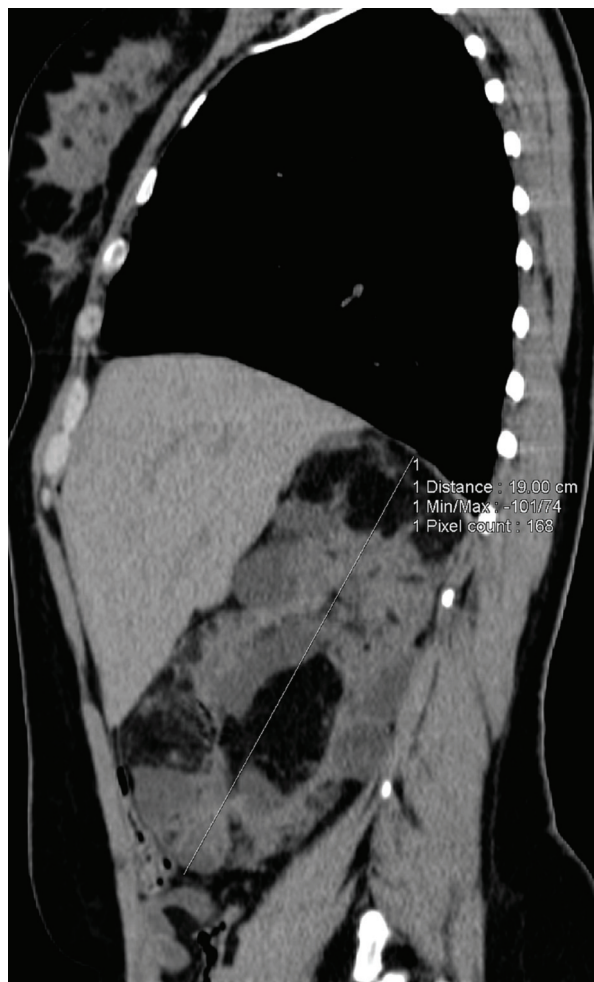
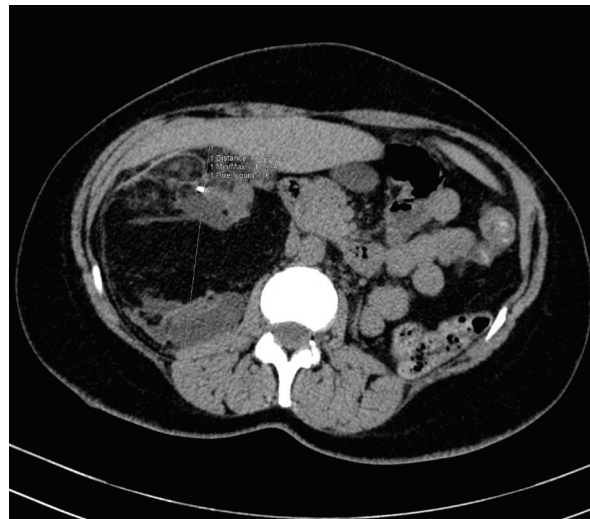


Figure 2

Thoracoabdominal CT scan (anteroposterior view) showing a giant angiomyolipoma before the beginning of treatment with everolimus (June 2014).



the following possible therapeutic options: right total nephrectomy with subsequent renal replacement therapy; right total nephrectomy and living-donor transplantation; or treatment with mTOR inhibitors. The patient refused the first two options, but accepted systemic therapy with mTOR inhibitors. In June 2014 she was started on everolimus 10 mg daily orally, and the drug was administered for 6 months. During the treatment phase, she was evaluated clinically and analytically every month. The treatment was well tolerated and there was none of the adverse effects reported with this drug. There was no change in the renal function, proteinuria or serum cholesterol levels, and blood levels of everolimus were within the therapeutic range (mean everolimus levels 7.0 ng/mL; therapeutic range 3-8 ng/mL).

After a six-month treatment period (as of January 2015), the patient underwent a thoracoabdominal CT scan to assess the efficacy of treatment with everolimus, and no changes in renal angiomyolipoma volume or pulmonary parenchymal changes were observed. There was a mild improvement in the facial angiofibromas. A brain MRI was not performed at this time point because of the patient refusal.

■ DISCUSSION

Angiomyolipoma is the most common renal tumour in TSC, and the main cause of morbidity and mortality⁹. Reducing tumoural volume, preventing haemorrhage and preserving renal function are the main goals of the treatment⁷. Angiomyolipoma of less than 4 cm in diameter needs regular ultrasound monitoring¹⁵. Total nephrectomy is only performed when uncontrolled haemorrhage³, non-functional kidneys causing refractory hypertension, or evidence of underlying malign transformation are present¹⁵. Partial nephrectomy is a therapeutic option using a nephron-sparing surgery⁹.

Over the years, selective arterial embolization has been the mainstay of treatment of renal angiomyolipoma because of its renal-sparing nature, and it has been used to treat or prevent emergent situations, such as uncontrolled bleeding or large tumours with a high risk of bleeding^{3,9}. Radiofrequency ablation is an elective procedure available to treat renal angiomyolipoma¹²⁻¹⁴. Castle *et al.* reported 15 patients with renal angiomyolipoma (not associated with TSC) treated successfully with RFA, with preservation of renal function and no evidence of radiographic recurrence for a mean follow up of 21 months¹⁴. It is more effective for solid renal masses measuring 1 to 3 cm. Its efficacy and safety for larger angiomyolipomas are still unproven¹²⁻¹⁴.

Patients with TSC develop new lesions during their lives and previously treated tumours tend to recur⁹. The awareness that mutations in TSC1 and TSC2 genes have a critical importance in the pathophysiology of the disease, over activating the mTORC1 pathway, has led to the development of systemic therapies for angiomyolipoma treatment⁷. The mTORC1 pathway inhibitors (sirolimus and everolimus) are potential drugs that have been successfully used in the reduction of renal angiomyolipoma volume^{6,8,9,11,16}. Moreover, there is clinical evidence that mTORC1 pathway inhibitors could be used in other TSC manifestations, including skin manifestations, epilepsy, cardiac rhabdomyomas and pulmonary lymphangiomyomatosis¹⁶⁻¹⁸. Reducing angiomyolipoma volume, preventing the development of new lesions, preventing the lesions bleeding, and delaying deterioration of kidney function are the goals of treatment with mTOR inhibitors¹⁹.

Several clinical trials in patients with TSC have suggested that sirolimus may reduce renal angiomyolipoma volume, but angiomyolipomas increased in volume after the therapy was discontinued²⁰⁻²³, and in one trial some patients had experienced serious adverse effects²³. Although there is some evidence supporting efficacy and safety of sirolimus in this setting, the drug does not have a Food and Drug Administration (FDA) approval for this indication²⁴, and larger trials are essential to define the risks and benefits of sirolimus, as well as its role in the treatment of renal angiomyolipoma associated with TSC²³.

The EXIST-2 trial, the first prospective, international, randomised, double-blind, placebo-controlled phase 3 study, has shown that the administration of everolimus 10 mg daily for 24 weeks resulted in a reduction of at least 50% of total angiomyolipoma volume in 42% of patients, compared to placebo, and the treatment was associated with an acceptable safety profile⁷. Everolimus is an oral derivative of sirolimus, with better bioavailability, and is the only mTOR inhibitor approved by the FDA and the European Medicines Agency (EMA) for the management of TSC manifestations, including renal angiomyolipomas²⁴. The EMA has given a conditional approval to everolimus, meaning that the drug requires more evidence about its long-term effects and the duration of the response to treatment²⁵. The FDA approved everolimus for the treatment of renal angiomyolipoma associated with TSC, but its effectiveness was based on the response rate evaluated at a median time of 8.3 months of follow-up. Longer follow-up is mandatory to determine long-term outcomes²⁶.

Tuberous sclerosis complex is a rare condition which is progressive by nature. Currently, there are many unanswered questions concerning treatment with everolimus: when to initiate?, what dose should be prescribed?, for how long should the therapy be maintained? In our study, treatment with everolimus was not associated with a decrease in renal angiomyolipoma volume. Whether this was partially due to the advanced disease stage, or whether subtle changes in a voluminous tumour may go undetectable by CT scan, cannot be ascertained by this study. Over the treatment period, no increase in tumour volume, no new lesions and no angiomyolipoma bleeding were observed, and extra-renal manifestations remained unchanged (except for mild

improvement in skin angiofibromas). These data suggest a stabilization of the disease during the treatment period. As no adverse effects were detected, it was decided to maintain everolimus therapy 10 mg daily with no stopping rules, while monitoring tumour growth.

Disclosure of potential conflicts of interest: None declared.

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Correspondence to:

Dr. Miguel Oliveira
Nephrology and Dialysis Unit, Centro Hospitalar Tondela-Viseu,
Avenida Rei D. Duarte, 3504-509, Viseu, Portugal.
E-mail: pmig.oliv@gmail.com