Case Report

iMedPub Journals
www.imedpub.com

Archives of Medicine
ISSN 1989-5216

2021
Vol. 13 No.12: 56

Use of Everolimus in Tuberous Sclerosis Related Renal Angiomyolipoma: Two Case Reports

Tuğrul Burak Genç[1]*, Sema Sezgin Göksu[1], Ahmet Ender Caylan[2], Ömer Kutlu[2], Ali Murat Tatlı[1] and Hasan Şenol Coşkun[1]

1 Department of Medical Oncology, Akdeniz University, Faculty of Medicine, Antalya, Turkey
2 Department of Urology, Akdeniz University, Faculty of Medicine, Antalya, Turkey

***Corresponding author:**
Tuğrul Burak Genç

drtugrulburakgenc@yandex.com

Department of Medical Oncology, Akdeniz University, Faculty of Medicine, Antalya, Turkey.

Citation: Genç TB, Göksu SS, Caylan AE, Kutlu O, Tatlı AM and Coşkun HS (2021) Use of Everolimus in Tuberous Sclerosis Related Renal Angiomyolipoma: Two Case Reports. Arch Med Vol. 13 No. 12: 56

Abstract

Tuberous sclerosis complex is a genetic disorder characterized by the growth of hamartomas virtually any organ in the body. It is a rare disease and caused by mutations in the TSC1 or TSC2 genes. Mammalian rapamycin target pathway inhibitors have proven efficacy in the treatment of the disease. Everolimus treatment is recommended in patients with renal angiomyolipoma associated with tuberous sclerosis complex, even if they are asymptomatic, in the presence of lesions of 3 cm or more.

In this article, we shared the clinical course of 2 patients with renal angiomyolipomas associated with tuberous sclerosis complex followed by everolimus.

The first patient was a 24-year-old male and the second was a 31-year-old female. Both cases diagnosed after ruptured angiomyolipoma

On admission of the first case, multiple renal angiomyolipomas with the largest diameter of 47 mm were detected. With a 10 mg dose of everolimus, an approximately 20% reduction in the lesion was observed in the 3-years follow-up. No drug-related side effects were detected.

In the second case, approximately 20 cm diameter of renal angiomyolipoma was detected at presentation. Everolimus was started at a dose of 10 mg, and the dose was reduced to 5 mg in the first year of treatment due to recurrent grade 2 stomatitis and grade 2 hematological side effects. The patient is followed up as stable disease in the second year.

In conclusion; everolimus is an effective and safe drug in the treatment of tuberous sclerosis-related renal angiomyolipomas. To our knowledge, it seems rational to continue everolimus treatment unless there are unmanageable side effects despite dose reduction and failure of RAML control.

Keywords: Everolimus; mTOR; Renal angiomyolipom; Tuberous sclerosis complex

Received: October 13, 2021; **Accepted:** December 01, 2021; **Published:** December 08, 2021

Introduction

Tuberous Sclerosis Complex (TSC) is a genetic disorder characterized by the growth of hamartomas virtually any organ in the body (mostly in the brain, skin, heart, kidneys, and lungs). Recent prevalences estimates, from Ireland and Taiwan, TSC of 1:14,000-25,000 in individuals, which is below from older estimates of 1:10,000 [1]. TSC is caused by heterozygous mutations in TSC1 or TSC2 genes [2].

Renal Angiomyolipomas (RAML) associated with Tuberous Sclerosis Complex (TSC-RAML) is characterized as multiple and commonly bilateral lesions that consist of blood vessels, smooth muscles, and adipose tissues. RAML develops in approximately 80% of patients with TSC and a major criterion for diagnosis [3]. Although it is defined as a benign lesion, it can be fatal due to bleeding and perforation, especially in lesions above 4 cm [4]. The most important goal in treatment is to protect kidney function and prevent complications that may cause mortality. Radical

surgical techniques such as total nephrectomy may be needed for life-threatening conditions, but nephron-sparing surgery should be performed for complications whenever possible.

Mammalian rapamycin target (mTOR) pathway inhibitors are non-invasive and reliable drugs that provide TSC-RAML volume control and reduce the rate of serious complications. The International tuberous sclerosis complex consensus conference held in 2012 recommended mTOR inhibitors as the first-line treatment for RAML when enlarged to 3 cm or more, even when asymptomatic [5] everolimus is the first drug that received U.S. Food and Drug Administration approval for this indication.

Case Report

We here in report the clinical course and treatment of two patients with giant RAML.

Case 1

24 years old male patient, diagnosed with tuberous sclerosis, epilepsy, hypogammaglobulinemia, hypertension, diabetes mellitus, autism and hypothyroidism. The patient was using intravenous immunoglobulin, levothyroxine sodium, nifedipine, vigabatrin, oxcarbazepine, lamotrigine, enalapril, clobazam, metformin, sertraline, risperidone and tmp-smx due to additional comorbidities. Three years ago, partial nephrectomy was performed due to ruptured renal angiomyolipoma (approximately 20 cm) in the right kidney. Postoperative computed tomography (CT) imaging showed bilateral multiple RAMLs which the largest one is 46 × 47 mm sized and an angiomyolipoma with a diameter of 26 mm in the left adrenal gland. Everolimus was started at a dose of 10 mg/day. The dominant mass in the kidney had regressed to 38 × 38 mm and the mass in the suprarenal gland to 22 x 21 mm in the first follow-up imaging after treatment, lesion size remained stable in subsequent follow-ups. Everolimus-related side effects were not detected during the follow-up in the patients and dose reduction was not required. Everolimus use continues in the 3rd year of follow-up **(Figure 1).**

Case 2

A 31-year-old female patient underwent partial nephrectomy due to ruptured RAML 14 years ago. The patient, diagnosed with TSC after surgery. 12 years after diagnosis, the patient was referred to the medical oncology clinic when a new giant RAML was detected. In the abdominal CT imaging, there were bilateral RAMLs which the largest one with a diameter of 20 cm and an angiomyolipoma 2 cm sized in the liver. Everolimus was started at a dose of 10 mg/day. Lesion size remained stable during two years of follow-up. The everolimus dose is continued as 5 mg/day due to recurrent grade 2 stomatitis and grade 2 neutropenia. No angiomyolipoma-related complications were detected during the follow-up period. Everolimus use continues in the second year of follow-up **(Figure 2).**

Discussion

Tuberous sclerosis is an autosomal dominant disorder caused by mutations that inactivate either TSC1 (encodes hamartin) or TSC2 (encodes tuberin) through a two-hit tumor suppressor

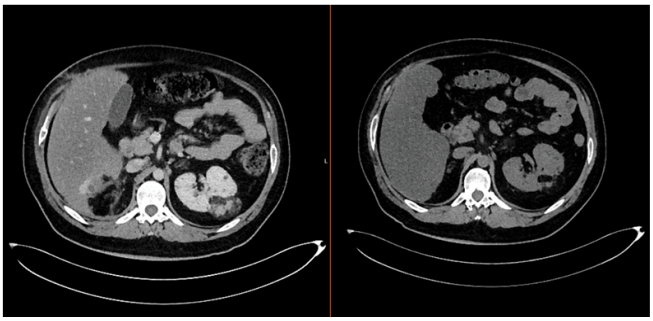

Figure 1 Case 1-CT images before and after everolimus.

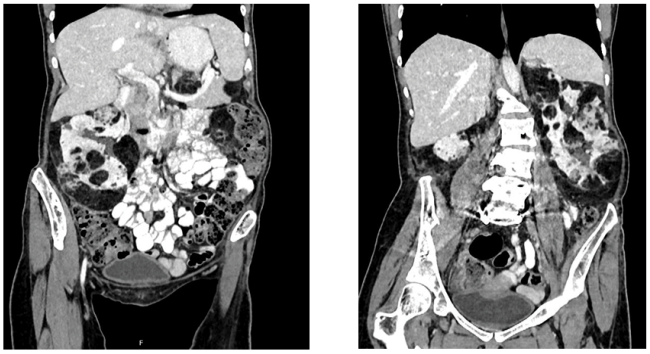

Figure 2 Case 2-CT images before everolimus therapy. Renal angiomyolipomas with a diameter of 20 cm and destructing the renal parenchyma.

gene mechanism [6]. Hamartin-tuberin complex inhibits the mTOR pathway that controls cell growth and proliferation, loss of function in these complex results in uncontrolled activation of mTOR. In vitro studies have shown that angiomyolipomas in TSC are due to increased intracellular phosphorylation as a result of this activation [7]. MTOR inhibitors suppress this cascade and reducing the angiomyolipoma volume or preventing its growth.

The EXIST-2 study demonstrated the superiority of everolimus over placebo for the treatment of TSC-RAML. In the study, 79 patients were randomized to the everolimus arm and 39 patients to the placebo arm. While 42% of patients were responsive to everolimus, progression was observed in all patients in the placebo arm. Everolimus reduced renal angiomyolipoma volume by ≥50% from baseline after median treatment duration of 38 weeks [6].

Post-hoc analysis of the EXIST-2 study showed that RAML lesions progressed after everolimus cessation, but there was no evidence of rapid regrowth [8]. Similar data was published in a single center Chinese study; in this study, RAML regressed somewhat during everolimus therapy but tended to increase in volume after the therapy was stopped [9].

When RAML grows to a size of >10 cm, they are referred to as 'giant' RAML. Data on the use of everolimus in giant RAML is limited in the literature, but it is seen that the drug is also effective in this group [6,9,10].

Especially in giant RAML cases, the risk of potentially life-threatening complications is high, therefore, patient selection for medical and surgical treatment should be made carefully and they should be followed closely.

In the two cases that we have shared in this article, partial nephrectomy was needed due to ruptured giant angiomyolipoma before the use of everolimus. In the first case, when a RAML over 3 cm was detected in post-op imaging, everolimus was initiated, reduction was observed in the size of the masses in the first year, and this response was maintained in 3-year follow-up. The second case was not followed for RAML for after surgery and giant RAML formation was observed within 12 years. There was no enlargement in tumor size, no new lesion formation, or tumor-related complications during follow-up with everolimus in both cases, and no drug-related grade 3 or higher toxicity was observed. Despite polypharmacy in our first case, no side effects due to everolimus and no drug interactions were experienced.

The main question to be answered in the follow-up of RAML cases is the duration of everolimus use. There is limited data regarding the decision of treatment duration in TSC-RAML cases. EXIST-2 trial supports a long-term benefit over approximately 4 years but current data show that RAMLs grows again after discontinued of everolimus [8,9,11]. Therefore, it is rational to use everolimus until toxicity or progression occurs but this decision actually raises a new question; is everolimus safe for long-term use?

The tolerability of everolimus in the EXIST studies was similar to that for other indications such as renal cell carcinoma, breast cancer, and transplantation. In the EXIST trials most frequently reported adverse events were stomatitis, diarrhoea, mouth ulceration, nasopharyngitis, upper respiratory tract infection, aphthous ulcer and pyrexia, most of these were grade 1 and 2 toxicities and grade 3 and above were rarely seen. Discontinuations due to adverse events were low [6,12]. Clinical management protocols for everolimus-related adverse events are well established. Everolimus use should be discontinued in the following cases; if there is failure in disease control (increase in lesion size after 6 months under treatment), unmanageable side effect despite drug dose reduction and progressive decrease in kidney function (glomerular filtration rate <30 mL/min or >3 g/L proteinuria) [13].

In conclusion; everolimus is an effective and safe drug in the treatment of TSC-RAML. To our knowledge, it seems rational to continue everolimus treatment unless there are unmanageable side effects despite dose reduction and failure of RAML control.

Clinical Trial Transparency

These case reports are compliant with all industry standards.

Ethics Approval

Patient's consents were received

Statement of Compliance

These case reports where applicable is compliant with all relevant laws and institutional guidelines. These case reports were written according to Declaration of Helsinki.

Declaration of Competing Interest

There are no financial and other conflicts of interest to disclose between the authors.

Acknowledgements

None.

References

1 Hallett L , Foster T, Liu Z, Blieden M, Valentim J (2011) Burden of disease and unmet needs in tuberous sclerosis complex with neurological manifestations: Systematic review. Curr Med Res Opin 27: 1571-1583.

2 Caban C, Khan N, Hasbani DM, Crino PB (2016) Genetics of tuberous sclerosis complex: İmplications for clinical practice. Appl Clin Genet 10: 1-8.

3 Ewalt DH, Sheffield E, Sparagana SP, Delgado MR, Roach ES (1998) Renal lesion growth in children with tuberous sclerosis complex. J Urol 160: 141-145.

4 Murray TE, Lee MJ (2018) Are we overtreating renal angiomyolipoma? A review of the literature and assessment of contemporary management and follow-up strategies. Cardiovasc Intervent Radiol 41: 525-536.

5 Krueger DA, Northrup H, Northrup H, Krueger DA, Roberds S, et al. (2013) International tuberous sclerosis complex consensus group. Tuberous sclerosis complex surveillance and management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 49: 255-265.

6 Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberg BA, Frost M, et al. (2013) Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): A multicentre, randomised, double-blind, placebo-controlled trial. Lancet 381: 817-824.

7 El-Hashemite N, Zhang H, Henske EP, Kwiatkowski DJ (2003) Mutation in TSC2 and activation of mammalian target of rapamycin signalling pathway in renal angiomyolipoma. Lancet 361: 1348-1349.

8 Bissler JJ , Nonomura N, Budde K, Zonnenberg BA , Fischereder M, et al. (2018) Angiomyolipoma rebound tumor growth after discontinuation of everolimus in patients with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis. PLoS One 13: e0201005.

9 Cai Y, Guo H, Wang W, Li H, Sun H, et al. (2018) Assessing the outcomes of everolimus on renal angiomyolipoma associated with tuberous sclerosis complex in China: A two years trial. Orphanet J Rare Dis 13: 43.

10 Toriu N, Mizuno H, Sawa N, Sumida K, Suwabe T, et al. (2018) Everolimus reduces the size of tuberous sclerosis complex-related huge renal angiomyolipomas exceeding 20 cm in the longest diameter. Case Rep Oncol 11: 258-267.

11 Sheth RA, Feldman AS, Paul E, Thiele EA, Walker TG (2016) Angiographic and volumetric effects of mammalian target of rapamycin inhibitors on angiomyolipomas in tuberous sclerosis. 8: 308-315.

12 Davies M, Saxena A, Kingswood JC (2017) Management of everolimus-associated adverse events in patients with tuberous sclerosis complex: A practical guide . Orphanet J Rare Dis 12: 35.

13 Yardley DA (2014) Adverse event management of mTOR ınhibitors during treatment of hormone receptor–positive advanced breast cancer: Considerations for oncologists. Clin Breast Cancer 14: 297-308.