

# Efficacy and safety of low-dose everolimus treatment for renal angiomyolipoma associated with tuberous sclerosis complex

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## Research

**Keywords:** everolimus, low-dose administration, renal angiomyolipoma, tuberous sclerosis complex, mammalian target of rapamycin inhibitor, oncological outcome, adverse event, renal dysfunction, low body weight

**Posted Date:** June 11th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-34526/v1>

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**Version of Record:** A version of this preprint was published at International Journal of Clinical Oncology on September 29th, 2020. See the published version at <https://doi.org/10.1007/s10147-020-01792-w>.

# Abstract

**Background:** Tuberous sclerosis complex (TSC) is a rare disease, with an autosomal dominant mode of inheritance, that results in systemic hamartoma. Renal angiomyolipoma (AML) is observed in 50-80% of TSC patients. Everolimus is recommended as an initial treatment for TSC-associated AML; however, few studies have investigated the efficacy and safety of low-dose everolimus therapy. In the present study, we evaluated the safety and efficacy of low-dose everolimus treatment in patients with TSC-associated AML with renal dysfunction or low body weight.

**Methods:** From January 2014 through December 2018, a total of 50 adult patients underwent everolimus treatment for AML associated with TSC. For patients with renal dysfunction (serum creatinine level  $\geq 1.5$  mg/dl) or low body weight (body weight  $< 35$  kg), 5 mg of everolimus was administered daily (low-dose group). For patients without renal dysfunction or low body weight, 10 mg of everolimus was administered daily (conventional-dose group). The treatment effects and adverse events (graded according to the Common Terminology Criteria for Adverse Events v5.0–JCOG) were compared between the two groups.

**Results:** There were 20 patients in the low-dose group, and 30 in the conventional-dose group. The average reduction rate of the AML volume in the low-dose group was 52%, whereas it was 60% in the conventional-dose group. No significant differences were found in the average reduction rate between the groups ( $P=0.24$ ). The average blood everolimus trough levels were  $7.7 \pm 3.1$  ng/mL in the low-dose group and  $12.2 \pm 5.7$  ng/mL in the conventional-dose group. The level was significantly higher in the conventional-dose group than in the low-dose group ( $P=0.004$ ). The incidences of stomatitis and irregular menstruation were significantly lower in the low-dose group than in the conventional-dose group ( $P=0.009$ ,  $P=0.045$ , respectively).

**Conclusions:** The present study demonstrates that low-dose everolimus treatment is safe and effective for TSC-associated AML. This treatment was well tolerated and adverse events were mild in all cases. Based on our results, low-dose everolimus can be considered a treatment option for patients with TSC-associated AML, especially for those who have renal dysfunction or low body weight.

## Background

Tuberous sclerosis complex (TSC) is a systemic disease with an autosomal dominant mode of inheritance, in which hamartomas form throughout the body, leading to the development of various organ disorders<sup>1</sup>. TSC is most often caused by mutations of the *TSC1* gene (which encodes hamartin), or *TSC2* gene (which encodes tuberin) located in chromosomes 9 and 16, respectively<sup>2,3</sup>. AML is the most frequent benign renal tumor and is observed in 50%-80% of TSC patients<sup>4</sup>. TSC-associated AML differs from sporadic AML, in that it frequently develops at multiple locations or bilaterally<sup>5</sup>. Most AML cases are asymptomatic and their renal function is normal<sup>6</sup>. TSC-associated AML is rarely observed in infancy, and it generally develops between the second and third decades of life<sup>7</sup>. When the tumor size is  $\geq 4$  cm, the growing speed is fast, and the incidence of hemorrhaging and hematuria increases<sup>5</sup>.

Approximately 30% of TSC patients die due to the aggravation of renal lesions<sup>8</sup>. For this reason, it is of the utmost importance that these lesions be treated and managed appropriately. The International Tuberous Sclerosis Complex Consensus Conference (ITSCCC) held in 2012 recommended mammalian target of rapamycin (mTOR) inhibitors as the first-line treatment for AML when lesions were enlarged to  $\geq 3$  cm, even when asymptomatic<sup>9</sup>. Transcatheter arterial embolization (TAE) and partial nephrectomy are recommended as second-line treatments<sup>9</sup>. The standard dose for everolimus for adult TSC-associated AML is 10 mg daily. The dose may be increased or decreased depending on the patient's condition and the trough level. However, there are quite a few patients who receive low-dose everolimus treatment due to renal dysfunction or low body weight. There have been few studies investigating the effects of low-dose everolimus in the treatment of TSC-associated AML. In this retrospective study, we investigated the effects and adverse events of low-dose everolimus in patients with TSC-associated AML.

## Methods

### Patients and study design

TSC-associated AML was defined according to the diagnostic criteria of the ITSCCC after discussions with an internist and a dermatologist. From January 2014 through December 2018, a total of 50 adult patients met the diagnostic criteria and underwent everolimus treatment for TSC-associated AML. This treatment was performed for AML  $\geq 4$  cm in size. The reduction ratio of AML was calculated according to the volume of AML measured on multi-slice helical CT scans for three-dimensional imaging. The volume of the AML was compared to the baseline volume, which was measured before the initiation of treatment. During treatment with everolimus, abdominal CT scans were obtained at three-month intervals. Adverse events were defined according to the Common Terminology Criteria for Adverse Events v5.0–JCOG (National Cancer Institute, Bethesda, MD, USA). The present study received approval from the institutional review board of JR Tokyo General Hospital (No. R01-22).

### Exclusion criteria

Patients with any of the following conditions were excluded from the present study: 1) poor respiratory condition due to lung lymphangiomyomatosis; 2) uncontrollable epileptic seizures (despite treatment with antiepileptic agents); 3) swallowing disorders; and 4) pregnancy. Patients who were unable to periodically visit the hospital were also excluded from the study.

### Everolimus treatment

For patients with renal dysfunction (serum creatinine level  $\geq 1.5$  mg/dl) or low body weight (body weight  $< 35$  kg), 5 mg of everolimus was administered daily (low-dose group). For patients without renal dysfunction or low body weight, 10 mg of everolimus was administered daily (conventional-dose group). We compared the treatment effects and adverse events of the low-dose and conventional-dose groups. The blood everolimus trough levels were measured in both groups. Examinations were performed every month after the start of treatment. During these examinations blood testing, urinalysis, and chest

radiography were performed and adverse events were assessed. KL-6 was measured to evaluate interstitial pulmonary disease. When an adverse event of Grade  $\geq 3$  was noted, the treatment was temporarily suspended. Everolimus could be resumed following the resolution of the adverse event.

## Statistical analyses

Wilcoxon's signed-rank test was used to compare the serial tumor volume measurements and adverse events due to everolimus.  $P < 0.05$  was considered to be significant.

# Results

## Patient characteristics

We analyzed 50 adult patients with TSC-associated AML who underwent everolimus treatment (Table 1). There were 20 patients in the low-dose group and 30 in the conventional-dose group. All of them met the diagnostic criteria for TSC. One patient in the low-dose group showed a performance status of 2 due to mental retardation and muscle weakness. In the low-dose group, there were 17 patients with renal dysfunction (serum creatinine level  $\geq 1.5$  mg/dl) and 3 with low body weight (body weight  $< 35$  kg). Three patients (15%) in the low-dose group and four (13%) in the conventional-dose group had AML  $\geq 10$  cm in diameter.

## Treatment efficacy

The median everolimus treatment periods were 17 months (range 10-33 months) in the low-dose group and 19 months (range 12-37 months) in the conventional-dose group. The volume reduction rate was calculated according to the AML volume after the start of treatment (the baseline AML volume was defined as 100%). Figures 1 and 2 show the largest rate of reduction from baseline in each of the cases. The average reduction rate of AML volume in the low-dose group was 52%, whereas it was 60% in the conventional-dose group. No significant differences were found in the average reduction rate between the groups ( $P=0.24$ ). The average blood everolimus trough levels were  $7.7 \pm 3.1$  ng/mL in the low-dose group and  $12.2 \pm 5.7$  ng/mL in the conventional-dose group. The level was significantly higher in the conventional-dose group than in the low-dose group ( $P=0.004$ ).

## Adverse events

Adverse events related to everolimus treatment in the two groups are shown in Table 2. Stomatitis and irregular menstruation were frequently observed in both groups. The incidence of these events was significantly lower in the low-dose group than in the conventional-dose group ( $P=0.009$  and  $P=0.045$ , respectively). The incidences of other events did not differ markedly between the two groups. Adverse events of Grade  $\geq 3$  were observed in 3 patients (10%) in the conventional-dose group, but in none of the low-dose group.

Abnormal everolimus treatment-related laboratory test values are shown in Table 3. For non-hematologic toxicities, the rate of elevation of the serum KL-6 level was significantly higher in the conventional-dose group than in the low-dose group ( $P=0.041$ ). Patients with elevated serum KL-6 levels were followed up carefully since such patients are at a high risk of developing interstitial lung disease (ILD). There was only one case of ILD in each group (Table 2). The incidence of other laboratory abnormalities did not differ markedly between the two groups. There were no laboratory abnormalities of Grade  $\geq 3$  in either group. Everolimus treatment has been continued in both groups, and the renal function has not been aggravated in any of them as of yet.

## Discussion

Recently, there have been an increasing number of reports on low-dose molecular-targeted drug therapies for renal cell carcinoma and breast cancer<sup>10,11</sup>. Murata et al. reported the effect of low-dose axitinib administration for metastatic renal cell carcinoma<sup>9</sup>. Chang et al. showed that low-dose everolimus treatment was effective for neonatal cardiac rhabdomyoma<sup>12</sup>. The advantages of low-dose treatment are sustained drug effects, minimization of adverse events with treatment, and a reduction in medical costs<sup>13</sup>.

The effectiveness of everolimus for TSC-associated AML has been demonstrated in the EXIST-2 and extension studies<sup>14,15</sup>. Everolimus treatment for TSC-associated AML rarely achieves complete remission<sup>14,15</sup>. The drug can shrink AML, but cannot cure it. Therefore, the patient must continue to take it for a long time. Several prospective studies have shown that the serum creatinine levels are increased in a significant proportion of patients receiving everolimus<sup>16,17</sup>. In some TSC patients, the renal function decreases after TAE or renal surgery. In addition, some patients become underweight due to severe developmental disorders. The administration of a conventional-dose of everolimus to these patients may further reduce their renal function. For these reasons, we retrospectively investigated the effects and adverse events of low-dose everolimus treatment for TSC-associated AML.

The average reduction rate of AML volume was equivalent between the low-dose and conventional-dose groups. The average blood everolimus trough level in the conventional-dose group was significantly higher than in the low-dose group. However, the recommended trough level of everolimus for TSC-associated AML is 5 to 15 ng/mL, and the average trough level of the low-dose group was within this range.

In the EXIST-2 extension study, the main adverse events of everolimus treatment were nasopharyngitis (43%), stomatitis (43%), and headache (30%). Adverse events of Grade  $\geq 3$  developed in 14% (16 of 112) of the cases. In our study, the incidences of stomatitis and irregular menstruation were relatively high in the conventional group (93% and 73%, respectively). Stomatitis in patients treated with everolimus, a frequently reported adverse effect, is often severe, and it may significantly reduce the patient's quality of life<sup>18</sup>. It is often necessary to reduce the dose of everolimus or to suspend administration altogether. Therefore, stomatitis with everolimus treatment is a major problem hampering continuous treatment. In

addition, several mTOR inhibitors have been shown to reduce serum testosterone levels in men and serum progesterone levels in women, and irregular menstruation subsequently occurs in women<sup>19-21</sup>. Since many patients with TSC-associated AML are young, it is necessary to take measures to prevent hypogonadism. The incidences of stomatitis and irregular menstruation were significantly lower in the low-dose group than in the conventional-dose group. These findings suggest that low-dose everolimus treatment for TSC-associated AML may minimize adverse events associated with treatment.

The present study has some limitations. First, this was a retrospective study, and everolimus was administered at the discretion of the treating urologist rather than via a prospective protocol. Second, this study did not include children. This is because the recommended dose of everolimus for pediatric TSC-associated AML is 3.0 mg/m<sup>2</sup> daily, but the dose differs among pediatric cases. Further studies on the effects and adverse events of low-dose everolimus treatment for pediatric TSC-associated AML are necessary.

## Conclusions

The present study demonstrates that low-dose everolimus treatment is safe and effective for TSC-associated AML. This treatment was well-tolerated and adverse events were mild in all cases. Based on our results, low-dose everolimus can be considered a treatment option for patients with TSC-associated AML, especially those who have renal dysfunction or low body weight. Further studies should be performed to broaden our knowledge on the safety and efficacy of low-dose everolimus for TSC-associated AML.

## Abbreviations

TSC: tuberous sclerosis complex; AML: angiomyolipoma; ITSCCC: International Tuberous Sclerosis Complex Consensus Conference; mTOR: mammalian target of rapamycin; TAE: Transcatheter arterial embolization; ILD: interstitial lung disease.

## Declarations

### Acknowledgments

We thank the patients and their families for participating.

### Authors' contributions

TH participated in the design of the study and drafted the manuscript. KE participated in data acquisition. MT participated in the design of the study and helped to write the paper. All authors read and approved the final manuscript.

### Funding

No external funding.

### **Availability of data and materials**

Data are available on reasonable request.

### **Ethics approval and consent to participate**

This study was approved by the institutional review board of JR Tokyo General Hospital (No. R01-22). All patients provided written informed consent before entering the study.

### **Consent for publication**

Not applicable.

### **Competing interests**

The authors of this article declare no conflict of interest.

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## Tables

Table 1. Baseline characteristics of 50 patients receiving everolimus treatment

<b>Characteristics</b>	<b>Low-dose group (n=20)</b>	<b>Conventional-dose group (n=30)</b>
Median age, years (range)	27 (20-51)	28 (20-54)
<b>Sex</b>		
Male/Female	9/11	15/15
<b>ECOG performance states</b>		
0/1/2	15/4/1	25/5/0
Renal dysfunction	17	0
Low body weight	3	0
<b>Kidney</b>		
Angiomyolipoma diameter		
≥4 to <10 cm	17	26
≥10 cm	3	4
<b>Skin</b>		
Facial angiofibromas	16	25
Hypometanotic macules	8	15
Ungual/subungual fibromas	7	12
Shagreen patch	6	11
Forehead plaque	5	9
<b>Brain</b>		
Cortical tubers	16	27
Subependymal nodules	11	14
Subependymal giant cell astrocytoma	3	5
<b>Others</b>		
Lung lymphangiomyomatosis	4	5
Retinal hamartoma	4	3
Liver angiomyolipoma	2	2

Table 2 Treatment-related adverse events

Event	Low-dose group N (%)	Conventional-dose group N (%)	<i>P</i> -value
Stomatitis	12 (60)	28 (93)	0.009
Irregular menstruation	3 (27)	11 (73)	0.045
Nasopharyngitis	5 (25)	12 (40)	0.365
Vomiting	3 (15)	8 (27)	0.490
Fatigue	2 (10)	6 (20)	0.450
Body weight loss	2 (10)	5 (17)	0.687
Diarrhea	2 (10)	4 (13)	1.000
Rash	2 (10)	4 (13)	1.000
Abdominal pain	2 (10)	3 (10)	1.000
Pruritus	1 (5)	2 (7)	1.000
Interstitial lung disease	1 (5)	1 (3)	1.000

## Figures

Table 3 Treatment-related laboratory abnormalities

Laboratory abnormality	Low-dose group N (%)	Conventional-dose group N (%)	<i>P</i> -value
<b>Hematologic toxicity</b>			
Anemia	2 (10)	6 (20)	0.450
Neutropenia	1 (5)	5 (17)	0.381
Thrombocytopenia	1 (5)	3 (10)	0.641
<b>Non-hematologic toxicity</b>			
Increased KL-6	4 (20)	15 (50)	0.041
Proteinuria	4 (20)	8 (27)	0.740
Hypercholesterolemia	3 (15)	4 (13)	1.000
Hematuria	3 (15)	3 (10)	0.672
Hypertension	2 (10)	3 (10)	1.000
Increased lactate dehydrogenase	2 (10)	1 (3)	0.556
Increased alkaline phosphatase	1 (5)	1 (3)	1.000

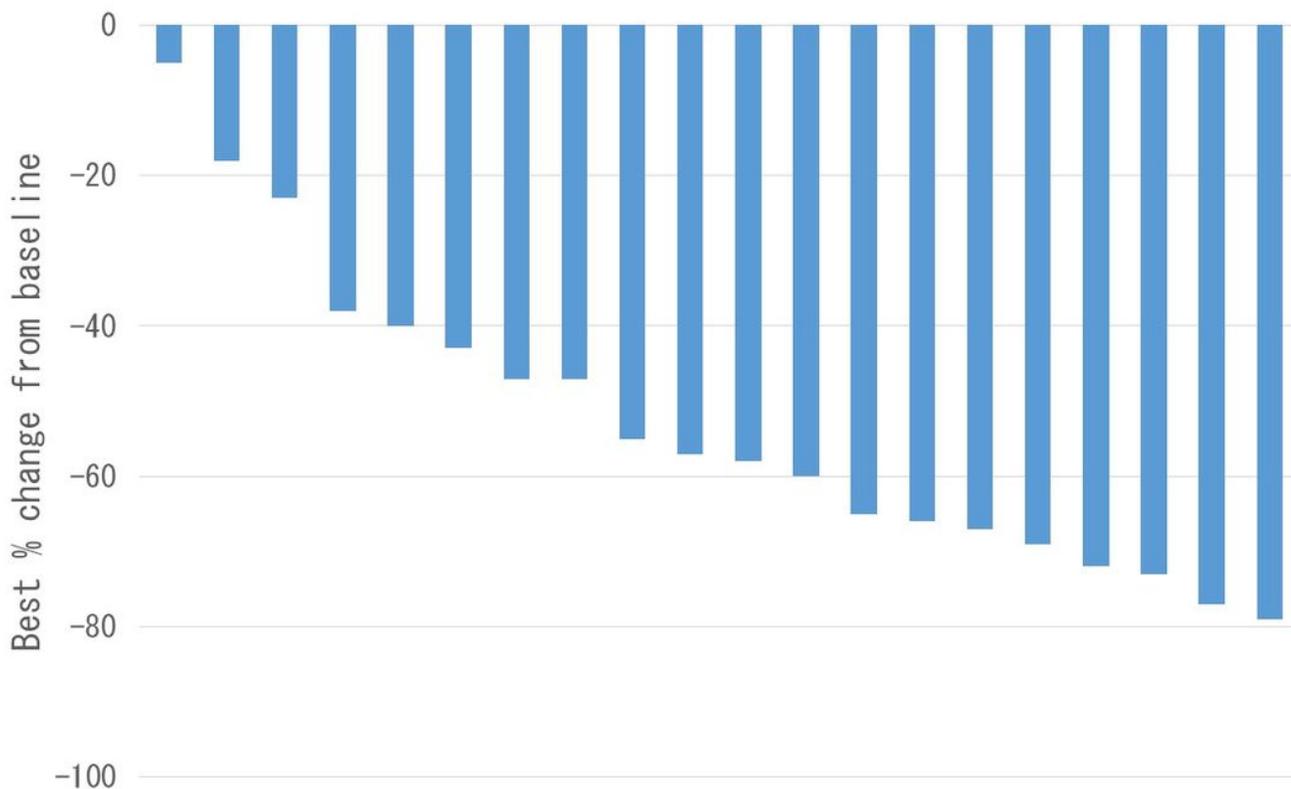
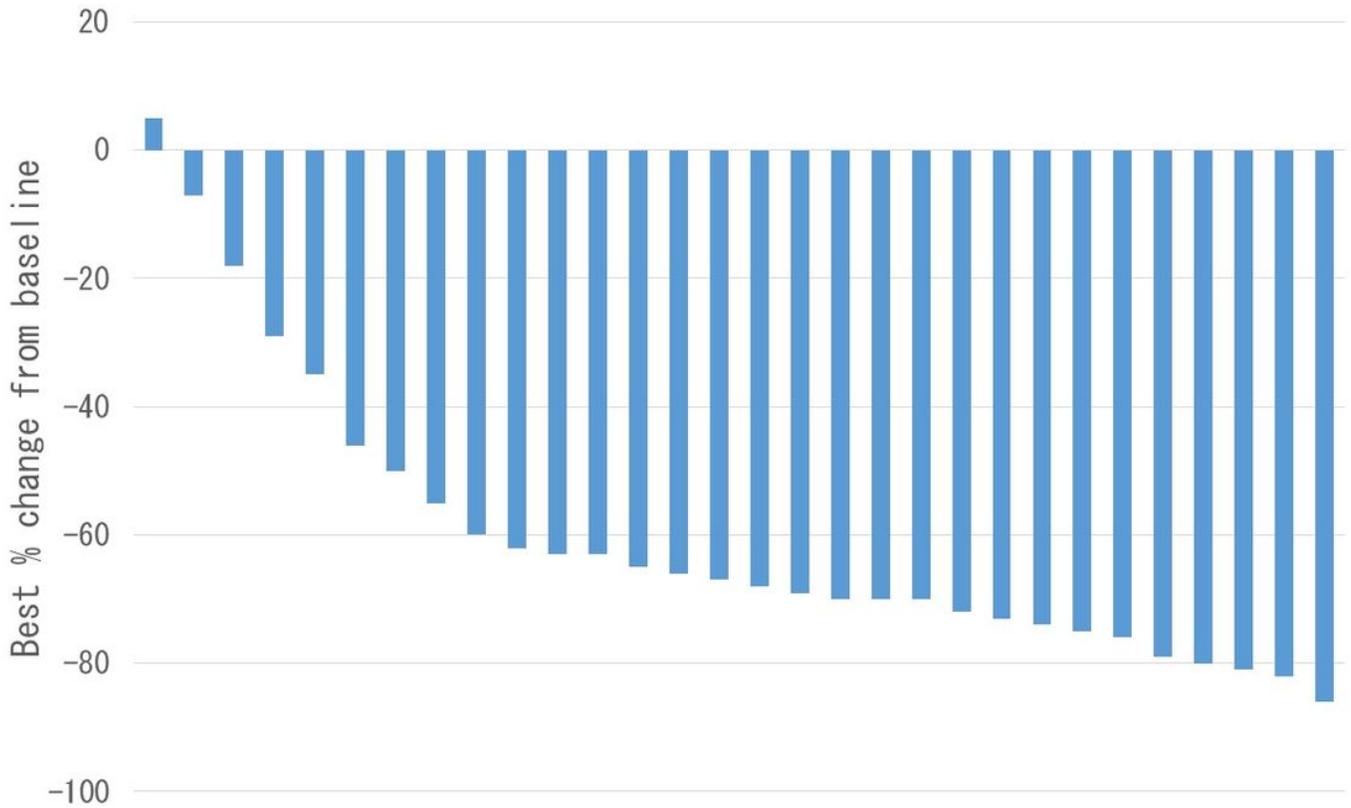


Figure 1

Best percentage change in the AML volume from baseline in the low-dose group. The AML volume decreased in all patients. The average reduction rate for all cases was 53%.



**Figure 2**

Best percentage change in the AML volume from baseline in the conventional-dose group. The average reduction rate for all cases was 60%. No significant difference was found in the average reduction rate between the low-dose and conventional-dose group (P=0.24).

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