THE ROLE OF EVEROLIMUS IN PATIENTS WITH TUBEROUS SCLEROSIS COMPLEX-ASSOCIATED MANIFESTATIONS: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Tuberous sclerosis or tuberous sclerosis complex (TSC) is a genetic disease caused by mutations in tuberous sclerosis complex 1 (TSC1) or tuberous sclerosis complex 2 (TSC2) genes that affects multiple organs such as the kidneys, brain, lungs, heart, and skin. Objective: This systematic review aims to assess the clinical value of everolimus for various manifestations in TSC patients. Methods: We searched PubMed, Cochrane Library, Clinical Trials (http://www.clinicaltrials.gov) and Google Scholar from January 2009 to December 2018. We included RCTs published in English, enrolled patients aged 0-65 years, with a definitive diagnosis of TSC on everolimus therapy for at least 18 weeks, medically stable and unlikely to require surgery during the trial. Two reviewers singly extracted data, assessed study quality, and applicability, and the strength of evidence for each study graded by consensus. Results: Four RCTs that met inclusion criteria assessed the effects of everolimus in TSC patients, and two RCTs reported the impact of everolimus on rate of tumor response (angiomyolipoma, skin lesion, and subependymal giant cell astroclytomas), tumor volume, tumor progression rate. These two RCTs revealed a higher percentage of tumor response, a significant reduction in tumor size and low tumor progression rate when compared to placebo. And two studies described the impacts of everolimus on neurological manifestations of TSC wherein one showed reduced frequency of TSC-associated seizures and no improvement in neurocognitive functioning or behavior change in the other. The most common everolimus-related adverse reactions were stomatitis and mouth ulceration. Conclusions: Everolimus produced a significant impact on the reduction of tumor size, angiomylolipoma progression rate, improved tumor response rate, reduced frequency of seizures, but no effects in neurocognitive functioning or behavior change found, and also everolimus increased the incidence of stomatitis and mouth ulcerations.

KEYWORDS: Everolimus, Tuberous sclerosis, Tuberous sclerosis-associated manifestations, Randomized controlled trials.

INTRODUCTION

Tuberous sclerosis complex (TSC) is a hereditary autosomal dominant multi-system disease, affecting 1–2 million people globally.[11,12] The primary clinical feature of TSC is development of benign tumor-like lesions in potentially all organ systems.[2][3] Currently, two genetic loci are mapping TSC; TSC1 (located in chromosome 9q34, encoding the protein hamartin) and TSC2 (located in chromosome 16p13.3, encoding the protein tuberin).[4][5] Tuberin and hamartin are widely expressed in all tissues, functioning as a tumor suppressor complex in the control of cell division and growth.[6][7]

Pathogenic mutations in one of the two genes (TSC1 or TSC2) cause impairment of the intracellular hamartin/tuberin-complex, leading to over-activation of the mTOR (mammalian target of rapamycin) signaling pathway resulting in uncontrolled protein synthesis and cell growth.[8][9]

Tumors of significant clinical attentions include those involving the brain, kidneys heart and lungs.[10]

The CNS is affected in more than 90% of individuals with TSC, with the presence of characteristic lesions such as cortical or subcortical tubers, subependymal nodules (SEN), subependymal giant cell astrocytomas (SEGA), and white matter radial migration lines (RML).[11,12] Neurological complications include obstructive hydrocephalus (due to SEGAs located near...
the foramen of Monroe), TSC-associated neuropsychiatric disorders (TAND) and epilepsy.\(^5\)\(^{[13]}\)

Renal problems in TSC, including angiomylipomas (which occur in 80% of people with TSC) and multiple renal cysts,\(^{[14]}\) comprise the second leading cause of premature death after severe intellectual disability.\(^{[15]}\)

Angiomyolipomas are benign tumors composed of smooth muscle, vascular, and adipose tissue.\(^{[16]}\) In the kidney, angiomyolipomas can cause severe issues with bleeding because of their vascular nature and can necessitate the need for dialysis and even renal transplantation.\(^{[17]}\)

Multiple renal cysts can be seen in people with TSC who have a TSC1 or TSC2 mutation or as part of a contiguous gene deletion syndrome involving the TSC2 and PKD1 genes.\(^{[18]}\)

Inhibiting mTOR kinase was thought to be a useful approach to systemic therapy for TSC because it to normalize dysregulated mTOR signaling in cells that lack normal hamartin or tuberin.\(^{[19]}\)\(^{[20]}\)

The mTOR inhibitors, everolimus has been shown to reduce renal and brain lesions size, and improve pulmonary function in TSC, and these compounds may also decrease seizure frequency.\(^{[21]}\)

The clinical application of mTOR inhibitors in TSC has provided one of the first examples of precision medicine in a neurodevelopmental disorder.\(^{[22]}\)

This systematic review aims to bring together clinical trials in this area to establish the clinical value of everolimus for various manifestations in TSC.

**Methods**

Our systematic review carried out with accordance to Cochrane handbook for systemic reviews of interventions\(^{[23]}\) and presented based on Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.\(^{[24]}\)

**Data Sources and Searches**

We searched for the Cochrane library, PubMed databases, and we also examined data from Clinical Trials (http://www.clinicaltrials.gov) and Google Scholar from January 2015 to December 2018 without restriction of language country or race.

Our search strategy included keywords: Randomized controlled trials, everolimus, and TSC TSC-associated manifestations. We searched all fields in PubMed and all text in Cochrane Library. When searching ClinicalTrials.gov, we used the term ‘Everolimus, and TSC’. Google search was conducted to find the randomized controlled trial (RCT) information unavailable from bibliographical databases.

**Study Selection**

Studies were chosen based on the following inclusion criteria: (1) RCTs (randomized control trials) involving patients with a definitive diagnosis of TSC on everolimus therapy versus placebo regardless of the dosage; (2) Patients aged 0-65 years old. Exclusion criteria were: case reports, case review, nonrandomized controlled trials, patients without TSC and patients with TSC but not on everolimus.

All analyses conducted based on previously published studies; thus, no ethical approval and patient consent were required.

We included studies that assessed one of the following findings: tumor volume, tumor progression rate, tumor response rate, the frequency of seizures, neurocognitive functioning or behavior and adverse reactions (stomatitis and mouth ulcerations).

**Data Extraction and Risk-of-Bias Assessment**

**Data Extraction**

First of all, we identified randomized controlled trials through title or abstract based on inclusion and exclusion criteria, and eligible studies extracted through reading abstract or full text. This process was performed by two reviewers (Dr. Lukwaro and Dr. Kasene) independently. Discrepancies resolved by discussion between the two reviewers, and unresolved disagreement referred to a 3rd reviewer (Dr. Xujun).

Data were extracted independently considering the following information from each study: lead author; publication year; participant characteristics; doses of everolimus, age, and significant adverse effects.

If the trials had more than two groups or factorial study designs and permitted several comparisons, we extracted only the data and information of interest reported in the original trials.

**Risk of bias assessments**

Two reviewers singly assessed the risk of bias using Cochrane risk of bias tool of randomized trials and judged each quality item as low risk, high risk or unclear risk.\(^{[24]}\) The elements used to evaluate bias in each study included random sequence generation, allocation concealment, blinding, incomplete data regarding the outcome, selective reporting, and other items (i.e., groups comparable at baseline, funder/association, and incomplete information in the text).

The included trials graded as low quality, high quality, or moderate quality based on the following criteria: (1) RCTs considered low quality if either allocation concealment or randomization assessed as a high risk of bias, despite the risk of other elements. (2) Studies regarded as high quality when both randomization and allocation concealment judged as a low risk of bias, and all other items as low or unclear risk of bias in a trial. (3) Studies were regarded as moderate quality if they unmet criteria for high or low-risk bias.
RESULTS

Literature Search

From the searches for RCTS, 286 eligible studies extracted from PubMed, Cochrane library database, Clinical trials. gov, and additional RCTs identified through Google and google scholar. We screened titles and abstracts of these RCTs for inclusions, and read full texts of 18 studies, and finally, the total number of 4 RCTs met the inclusion criteria. Figure 1 These studies assessed the effects of everolimus on TSC-associated manifestations.

Study characteristics

Table 1: Summarizes the attributes of all the included 4 RCTs. The participants in all RCTs were patients with TSC (0-65 years old) and on everolimus therapy. The outcomes measuring the effects of everolimus were tumor volume, progression rate, response rate, the frequency of seizures, neurocognitive functioning or behavior, and adverse reactions (stomatitis and mouth ulcerations).
<table>
<thead>
<tr>
<th>Study, Year</th>
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<th>Study design</th>
<th>Study participants (n)</th>
<th>Median Age(year)</th>
<th>Median dose (mg/m²)</th>
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<th>Key findings</th>
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</thead>
<tbody>
<tr>
<td>Bissler et al. [25]</td>
<td>Everolimus versus placebo</td>
<td>RCT[1], a double-blind, placebo-controlled trial</td>
<td>118</td>
<td>31</td>
<td>10</td>
<td>NA</td>
<td>Reduction in AMLs volume with an acceptable safety profile.</td>
</tr>
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<td>Franz et al. [26]</td>
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<td>117</td>
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<td>Reduction in tumor volume, improved tumor responses in SEGAs[2] and low progression rate of renal AMLs.[3]</td>
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<td>RCT-double blind, placebo-controlled trial</td>
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<td>Krueger et al. [28]</td>
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<td>47</td>
<td>12.68</td>
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<td>1.32</td>
<td>No significant improvement in neurocognitive functioning or behavior</td>
</tr>
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</table>

[1] RCT=Randomized control trial  
[2] SEGAs= Subependymal giant cell astrocytomas  
[3] AMLs= Angiomyolipomas

**Assessment of risk of bias**  
All four studies were randomized, double-blinded, placebo-controlled trials. All four studies are seen as moderate in quality as shown in Figure 2 (A and B) as the category of other bias regarded as high risk of bias due to funding from drug companies. The insufficient number of RCTs included prevented the assessment of publication bias using the Funnel plot technique.

**Figure 2A**

![Cochrane risk of bias](image)

Figure 2: Cochrane risk of bias: (A) Graph and (B) Summary.
Figure 2B

**Synthesis of results from individual studies**

**Tumor volume, progression rate, and response rate**

Two RCTs included in our systematic review concluded that everolimus has a remarkable impact on tumor volume, progression rate, and tumor response rate.

According to Bissler et al.[25], Angiomyolipoma (AMLs) response rate was 42% (33 of 79 patients) for everolimus compared with 0% (0 of 39 patients) for placebo (difference 42%).

The median time to angiomyolipoma response for everolimus was 2.9 months.

At week 24, 55% (39 of 71) of everolimus patients had at least a 50% reduction in the sum of volumes of target AMLs lesions from the baseline compared with 0% (0 of 33) of placebo patients. Most everolimus patients had substantial decreases in percentage change from baseline in the sum of volumes of target angiomyolipoma lesions. All angiomyolipoma responses were ongoing for between 10 and 85 weeks at the time of the data cutoff.

Everolimus was superior to placebo in time to angiomyolipoma progression.

Angiomyolipoma progressions noted in three everolimus patients (4%) and eight placebo patients (21%). No patient achieving an angiomyolipoma response had progressed at the data cutoff date. Estimated progression-free rates for everolimus and placebo, respectively, were 98% and 83% at six months, and 92% and 25% at 12 months. Skin lesions associated with TSC were present at baseline in 114 patients. Everolimus had a significantly higher skin lesion response rate of 26% (20 of 77 patients) compared to 0% (0 of 37) in the placebo group. At the data cutoff, skin lesion responses were ongoing in the 20 everolimus patients who had a skin lesion response (range 10–84 weeks).

Franz et al.[26] report SEGA response rate of 57.7%. The median time to SEGA response was 5.32 months and ranged from 2.5 to 33.1 months. The median reduction from baseline in total SEGA volume and the proportion of patients achieving a 50% reduction in SEGA volume improved slightly over time.

Thirteen patients (11.7%) had progression of SEGA at any time during the trial. Only one of these TSC patients discontinued everolimus treatment due to SEGA progression. For six patients, SEGA progression was detected at the end-of-treatment visit after discontinuation of everolimus for other reasons.
(completed treatment \([n = 2]\), adverse effects \([n = 2]\) noncompliance \([n = 1]\), withdrew consent \([n = 1]\)). In the other six patients, although SEGA progression was seen, everolimus was continued at the discretion of the investigator. Five of the 13 patients with SEGA progression had attained response before progression. Duration of SEGA response for all responders ranged from approximately 5.1 to 53.3 months. The progression-free survival rate at three years after everolimus treatment initiation was 88.8%. No patient required surgical interventions due to SEGA progression during the trial.

In Renal Angiomyolipoma Response rate; Of the 41 patients with one target renal angiomyolipoma at baseline, 30 patients achieved a response rate of 73.2%. The median time of renal angiomyolipoma response was 42.3 months. The median percentage reduction in the total volume of target angiomyolipoma lesions was 74.3%, with a decrease in median volume from 14.65 cm\(^3\) at baseline to 4.35 cm\(^3\). More than 80% of patients experienced a reduction in renal angiomyolipoma volume of 50% at week 24, and this level of response continued over the trial period. No new angiomyolipoma lesions and instances of bleeding occurred.

In Skin Lesion Response; 105 patients had one skin lesion at baseline, the rate of skin lesions response was 58.1% \((61 \text{ of } 105\), with nine patients (8.6%) experiencing a full clinical response and 52 (49.5%) encountered partial response. More than 50% of patients demonstrated a response to everolimus treatment; nearly one-third reached full or partial response within 12 weeks, with responder rates increasing steadily through week 192. Three of the 61 responders (4.9%) encountered skin lesions progression, ranging from 2.3 to 55.5 months.

Frequencies of seizures, neurocognitive functioning, and behavior changes
French et al.\(^{[27]}\) report the median percentage in reduction of seizure frequency was 14-9%. Everolimus was associated with a significantly higher response rate (33 of 117 patients in the low-dose group, response rate 28-2% and 52 of 130 patients in the high-dose group, response rate 40-0%) and a significantly higher median percentage reduction in seizure frequency (in the low-exposure group, 29-3%, and in the high-exposure group, 39-6%). The odds of achieving a 50% or more significant reduction in seizure frequency was 2-2-times higher for low-exposure everolimus than placebo and 3-9-times higher (2-1–7-3) for high-exposure everolimus than for placebo. The seizure-free rate was 0-8% (one patient) for the placebo group, 5-1% (six patients) for the low-dose everolimus group, and 3-8% (five patients) for the high-dose everolimus group. The median number of free seizure days (per 28-day period) increased from baseline by 2-0 in the low-dose group and 4-0 days in the high-dose group, compared with 0-5 days in the placebo group. We noted a decrease in seizure frequency with everolimus treatment among multiple seizure types and the seizure reduction findings were virtually unchanged when generalized onset seizures confirmed by EEG.

Krueger et al.\(^{[28]}\) examined change scores from baseline for multiple neurocognitive and behavioral domains; almost all assessment measures failed to illustrate significant differences between the two groups at the end of 6 months. When comparing treatment to placebo, only the CANTABStockings of Cambridge (SOC) (objective performance measure of executive function) and SRS Social Cognition (parent rating of social behavior) were significant. The more favorable outcome on SOC associated with placebo than everolimus. Analysis of individual responses revealed that most individuals in the everolimus group and all in the placebo group improved compared to baseline on the SOC.

For the SRS, those in the everolimus group were more likely to be reported by caregivers to improve social cognition versus the placebo group.

No changes in executive function or academic performance although multiple subdomains of socialization and behavior showed differences with everolimus treatment, including the SRS Social Cognition, BASC2 Externalizing Problems, and SDQ Total Difficulties scores. The quadratic analysis identified a trend for improvements at three months that worsened by six months for SRS Social Cognition and Social Communication.

Adverse reactions (stomatitis and mouth ulcerations)
Franz et al.\(^{[26]}\) report 99.1% of all patients experienced an AE during this long-term study. The emergence of patients with adverse effects was high in the first year and decreased each subsequent year. Most of the patients (89.2%) experienced ≥1 adverse effect that was suspected of being related to everolimus treatment. The most common adverse effect suspected to be treatment-related in >10% of patients were stomatitis (43.2%), mouth ulcer (32.4%), pneumonia (13.5%), hypercholesterolemia (11.7%), blood cholesterol level increase (11.7%), pyrexia (10.8%), and nasopharyngitis (10.8%). Total of 101 patients (91.0%) required ≥1 dose reduction or interruption during the trial. The most common reason for dose reduction or interruption was an AE \((n = 80 \text{ [72.1%]}\)). In total, eleven patients (9.9%) experienced an AE that led to discontinuation.

Bissler et al.\(^{[25]}\) also report the main adverse effects in patients on Everolimus treatment group and placebo group were stomatitis (48% [38 out of 79 patients], 8% [3 of 39 patients], respectively), nasopharyngitis (24% [19 out of 79 patients] and 31% [12 out of 39 patients]), and acne-like skin lesions (22% [17 out of 79 patients] and 5% [2 of 39 patients]). Adverse effects leading to discontinuation occurred in 4% (three) of everolimus patients and 10% (four) of placebo patients.
Krueger et al.\textsuperscript{(21)} also report stomatitis/aphthous ulcers, was the most common AE (28% overall). Infections (mainly URI) and neurological complaints (headaches) were the only other AE accounting for more than 10% of all reported AE. Serious AE (SAE) were infrequent, and the first SAE was due to pneumonia that resolved with antibiotic treatment. The other SAE consisted of hospitalizations for pyelonephritis and behavioral/personality changes, and in each case treatment with study drug was resumed after resolution of the SAE.

French et al.\textsuperscript{(26)} adverse effects occurred in 13 (11%) patients in the placebo group, 21 (18%) in the low-dose group, and 31 (24%) in the high-exposure group. Serious adverse events reported in three (3%) patients who received placebo, 16 (14%) who received low-dose everolimus, and 18 (14%) who received high-dose everolimus. Adverse events led to everolimus treatment discontinuation in two (2%) patients in the placebo group versus six (5%) in the low-dose group and four (3%) in the high-dose group.

**DISCUSSION**

Tuberous sclerosis (TSC) is a severe disease characterized by the formation of multiple hamartomas.\textsuperscript{(29)} It is best known for cutaneous and neurologic abnormalities, and the earliest patients reported with TSC were all developmentally disabled, but it has only slowly become apparent that affected individuals may have average intelligence, may have few fits, and skin lesions. Most clinical reports concentrate on affected individuals seen because of medical complications, usually neurological manifestations.

Because of its striking variability of clinical expression and severity, the diagnosis of tuberous sclerosis complex can be difficult, especially in young individuals or in those with subtle findings.\textsuperscript{(30),(31)} The genetics and biologic mechanisms of tuberous sclerosis complex are not nearly as straightforward as once believed. For these reasons, the diagnosis of tuberous sclerosis complex can be challenging.\textsuperscript{(32)}

The neurological manifestations of TSC are particularly challenging and include infantile spasms, intractable epilepsy, cognitive disabilities, and autism.\textsuperscript{(33),(34)}

An increased understanding of the role of the mTOR signaling pathway plays in TSC has been a significant step in identifying the therapeutic potential of mTOR inhibitors such as everolimus.\textsuperscript{(19),(35),(36)}

In our systematic review, we evaluated the impact of Everolimus on TSC associated manifestations. Four studies met our inclusion criteria and integrated into our research, the risk of bias was assessed by Cochrane risk bias tool\textsuperscript{(24)}, all of which had a low risk of bias and thus increased the reliability of the results.

Everolimus produced a significant reduction in tumor volume, angiomyolipoma progression rate and improved tumor response rate.

Franz et al.\textsuperscript{(20)} observed SEGAs response rate increased to 58% over approximately four years of treatment, indicating that the tumor response is related to treatment duration.

The proportion of TSC patients with a clinically significant >50% reduction in SEGAs volume generally improved over time, indicating that clinically significant SEGAs reductions persisted. The SEGAs progression rate was relatively low (~12%), and some patients continued everolimus despite the progress of SEGAs because they were attaining clinical benefit. Because TSC affects multiple organ systems, the effects of everolimus were also significant in patients with renal skin lesions and angiomylipoma. In this study, increasing and sustained improvement in skin lesions and reductions in renal angiomylipoma volume were substantial, providing evidence of a broad clinical impact of systemic treatment with everolimus in patients with TSC. The evidence examining the use of oral everolimus for TSC has shown that the drug class has the potential for multisystemic impact in TSC not only in treating renal angiomylipomas, but also TSC-associated seizures, and other TSC manifestations.

Also, Bissler et al.\textsuperscript{(25)} report everolimus was more effective than placebo in angiomylipoma response rate, skin lesions response rate and time to angiomylipoma progression. At week 24, over half the everolimus patients had at least a 50% reduction from baseline in target angiomylipoma volume, whereas no placebo patients had volume reductions of 50% or more.

Our systemic review also evaluated the Frequency of seizures and neurocognitive functioning or behavior and revealed a significant reduction in TSC-associated seizures.

French et al.\textsuperscript{(27)} findings demonstrate that everolimus treatment of mixed-type seizures in patients with TSC, despite the increased baseline burden of seizures in these individuals, can lead to a clinically significant reduction in the frequency of seizures with a favorable benefit-risk ratio that improves with ongoing treatment. Everolimus, a disease-modifying drug aiming at the underlying molecular pathology of TSC, represents a new treatment choice for patients with treatment-resistant seizures associated with TSC. However, Krueger et al.\textsuperscript{(28)} report no effects in neuropsychological, academic skills or adaptive behavior in patients on everolimus.

Finally, we assessed the safety of everolimus and the majority of adverse effects were mild to moderate and well tolerated. The most common adverse effects (AE) in all studies were stomatitis and mouth ulcerations.\textsuperscript{(25–28)} In general, the majority of AEs associated with the
everolimus are linked to the immunosuppressive effect of this drug class and include mucositis, aphthous ulcers, fatigue, rash, anorexia, gastrointestinal effects such as nausea and diarrhea, arthralgias, thrombocytopenia, and effects on lipid metabolism.[37,38] In most cases, these adverse events are self-limiting and are manageable by dose reductions or cessation.[39] Potentially severe adverse events may include upper respiratory tract infections as well as noninfectious pneumonitis and a dramatic increase in serum cholesterol and lipoprotein levels, which may require dietary adjustment or the use of cholesterol-lowering medication.[40,41]

In summary, Everolimus have a significant impact in treating patients with TSC-associated manifestations by reducing tumor size, angiomyolipoma progression rate, the frequency of seizures and improving tumor response rate, however, has no significant effects in improving neurocognitive functioning or behavior in patients with TSC, also everolimus increased the incidence of stomatitis and mouth ulcerations.

We also, observed that the included studies failed to provide sufficient evidence on the correlation between everolimus treatment response and specific clinical features or types of mutations. And time for initiation of everolimus therapy and optimal treatment duration in patients with TSC-manifestations was not well established.

Our systematic review indicates that everolimus might be a good option on controlling TSC-associated manifestations, particularly on neurological and renal events but more attention should be on the risk of adverse effects.

We hypothesize that starting the treatment at an early age, possibly even at infancy, might prevent the development of tumors, epilepsy, and other disease manifestations associated with TSC.

Limitation: Some RCTs conducted as an open-label design in the extension phase thus may not adequately assess other clinical end-points, and all the included RCTs were sponsored by with drug companies which might introduce some potential bias.

CONCLUSION

With the rapidly increasing knowledge on the mTOR pathway concerning TSC, the future use of everolimus in the treatment of TSC is likely to become well established. The positive effect that everolimus has on a wide variety of TSC disease manifestations makes these drugs a potentially favorable treatment option. In light of the promising clinical efficacy reported, we anticipate that everolimus can be a useful treatment option in TSC, and have the potential to be a disease-modifying therapy in patients with the disease. Further data from larger, prospective trials will help to establish the clinical efficacy, optimal dosage regimens, and safety profile of everolimus in TSC patients, and more clearly define their role in this setting.

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