CADTH

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Sirolimus and Everolimus for the Treatment of Tuberous Sclerosis Complex: A Review of the Clinical Effectiveness

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	November 20, 2017
Report Length:	19 Pages

CADTH

Authors: Shirley S. T. Yeung, Charlene Argáez

Cite As: Sirolimus and everolimus for the treatment of tuberous sclerosis complex: clinical effectiveness. Ottawa: CADTH; 2017 Nov. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Context and Policy Issues

Tuberous sclerosis complex (TSC) is a genetic disease that results in the development of non-malignant tumours across multiple organ systems including the brain, kidneys, heart, lungs and skin.[1,2] The incidence of TSC is approximately 1 in 5000 to 10000 in live births and it is caused by a mutation in either the TSC1 or TSC2 gene.[2] The clinical manifestations of TSC varies greatly among patients where some may experience only dermatological features but others may experience serious neurological manifestations including seizures.[3] TSC1 and TSC2 are involved in mammalian target of rapamycin (mTOR) cell signaling.[2]

The management of TSC depends on the clinical signs and symptoms of each individual patient.[3] Surgical removal of tumours is recommended if the patient is a good candidate, and if not, mTOR inhibitors may be used for treatment.[3] Drugs like sirolimus and everolimus are inhibitors of mTOR, which is believed to slow the progression of such tumours in patients with TSC.[1]

The Canadian Drug Expert Committee (CDEC) recommended 'do not list' everolimus in Canadian public drug formularies for two indications: 1) the treatment of renal angiomyolipoma associated with TSC and for 2) the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with TSC in 2013 and 2015, respectively.[4,5] For the treatment of renal angiomyolipoma, CDEC recommended 'do not list' because it was unclear if the reduction in angiomyolipoma size resulted in a reduction in bleeding complications, avoidance of surgery, or preservation of renal function.[4] The recommendation not to list for the treatment of SEGA in patients with TSC was based on one randomized controlled trial that demonstrated a reduction in tumour size but did not provide additional evidence of clinically relevant benefits.[5,6] However, studies have been published since the CDEC recommendations that evaluate everolimus in patients with TSC.[7,8]

The purpose of this report is to summarize and appraise the available evidence, published since the CDEC recommendations, that evaluates the clinical effectiveness and safety of sirolimus and everolimus for patients with TSC and how these agents affect their clinical symptoms.

Research Questions

1. What is the clinical effectiveness of sirolimus for the treatment of tuberous sclerosis complex?
2. What is the clinical effectiveness of everolimus for the treatment of tuberous sclerosis complex?

Key Findings

Eight publications were identified including four systematic reviews, two RCTs, a subgroup analysis of an RCT, and one cohort study. The evidence suggests that treatment with

everolimus or sirolimus demonstrated a better response rate when compared to placebo for symptoms of TSC including reduction in cardiac rhabdomyolipoma, seizure frequency, and renal angiomyolipoma. Three unique primary studies were identified for everolimus and one study was identified for sirolimus. However, the studies were conducted in small sample sizes and have a follow-up of up to one year, making it difficult to understand the long term effectiveness and safety profile of these agents.

Common adverse events include stomatitis, mouth ulcerations, nasopharynitis and upper respiratory tract infections and generally occur in at least 15% of those who are treated with everolimus or sirolimus which may result in discontinuation or dose reduction of the drug, likely requiring frequent monitoring and assessment.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit the retrieval by health technology assessments, systematic reviews, and meta-analyses, randomized controlled trials, and non-randomized studies. A narrower search focused on the pediatric population did not make use of methodological filters. The search was limited to English language documents published between January 1, 2007 to October 23, 2017.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with tuberous sclerosis complex
Intervention	Q1: Oral sirolimus (rapamycin) Q2: Oral everolimus (RAD001, Afinitor)
Comparator	Q1 – Q2: Surgery (neurosurgery or other surgeries); placebo; compared to each other (sirolimus vs. everolimus); standard of care
Outcomes	Clinical effectiveness (symptom reduction [e.g. tumour size reduction, reduction in seizure frequency, neurocognitive development], safety [i.e. adverse events])
Study Designs	Systematic review, meta-analyses, randomized controlled trials, non-randomized studies.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2013 due to the availability of CDEC recommendations. Studies that were already included in any of the systematic reviews or

were part of the evidence considered by CDEC were excluded. Studies that considered topical formulations were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using AMSTART tool [9] and randomized studies were critically appraised using Downs and Black checklist.[10] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 350 citations were identified in the literature search. Following screening of titles and abstracts, 291 citations were excluded and 59 potentially relevant reports from the electronic search were retrieved for full-text review. Five potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 56 publications were excluded for various reasons, while eight publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Details of the individual study characteristics are provided in Appendix 2.

Study Design

Four systematic reviews (SR) were identified for the use of rapamycin or rapalogs for patients with tuberous sclerosis complex (TSC) and they were published in 2016 and 2015.[1,11-13] One of the SR included studies published up to August 2013 and reported four non-randomized single-armed trials evaluating efficacy and safety of sirolimus for renal angiomyolipoma associated with TSC.[13] Another SR included all types of non-randomized studies that evaluated sirolimus and its analogs in the reduction of TSC-associated tumours.[11] This SR reported results of four case reports and four single-armed studies.[11] Neither of these SRs identified studies examining the comparators of interest for this report and are therefore not further discussed.[11,13] Between the other two SRs, the studies span from 2006 to 2013.[1,12] One SR included only randomized or quasi-randomized trials while the other included case reports, case series and also one randomized controlled trial.[1,12] The SR conducted by Sasongko et al. consisted of all adult patients [1] while the SR conducted by Yang et al. included pediatric patients.[12] Patients in both SRs were required to be diagnosed with TSC.[1,12]

Three publications were identified with two unique randomized controlled trials (RCTs), one subgroup analysis of an RCT, and one cohort study that compared the treatment of everolimus to placebo.[7,8,14] One study was a cohort study, completed in 2017, that examined patients with cardiac rhabdomyoma associated with TSC who were treated with everolimus compared to historic controls who received no treatment.[7] The study conducted by French et al. in 2016 was a double blind RCT comparing everolimus to placebo for the reduction of seizures after 12 weeks of treatment.[8] Kingswood et al.[14] conducted a subgroup analysis of patients with angiomyolipomata in EXIST-1, a double-blind, randomized placebo controlled trial comparing everolimus to placebo.[6] The EXIST-1 trial was captured in the selected systematic reviews and is not described separately.

One study was identified evaluating the use of sirolimus compared to placebo for children in a randomized, placebo-controlled, crossover trial by Overwater et al. in 2016.[15]

Country of Origin

The investigators were from Malaysia for the Cochrane systematic review of rapamycin or rapalogs compared to placebo[1] and China for the second SR.[12] The cohort study was conducted in Canada[7] and the cross-over trial was in the Netherlands.[15] The other two RCTs were conducted across multiple countries.[8,14]

Patient Population

The Cochrane review conducted by Sasongko et al. specifically reviewed studies in adults, with the two studies evaluating oral everolimus focused on angiomyolipoma.[1] The other SR specifically searched for studies that were in the pediatric population, with different patient indications included.[12] Both SRs only included studies where patients have a definitive diagnosis of TSC.

The Aw et al. study looked at four neonates with TSC and cardiac rhabdomyomas who received everolimus and they were compared to historic controls who received no treatment.[7] Overwater et al. evaluated 23 children between 3 months to 12 years old with a definite clinical diagnosis of TSC and at least 1 epileptic seizure weekly and resistant to at least two anti-epileptic drugs with 48% male in the entire trial.[15] One RCT enrolled 366 patients with a confirmed diagnosis of TSC and treatment resistant epilepsy.[8] The median age was 10.1 years old with a range of 2.2 to 56.3 years old and 51.9% male.[8] Kingswood et al. conducted a subgroup analysis of the EXIST-1 RCT[6] and considered the group of patients with renal angiomyolipoma and included 44 patients aged 4.5 years old to 23.9 years old.[14]

Interventions and Comparators

The Cochrane review included studies that compared everolimus and topical sirolimus while the other SR included studies of everolimus and both topical and oral sirolimus.[1,12]

Three publications compared everolimus to placebo[7,8,14] while one study compared oral sirolimus to placebo.[15]

Outcomes

The primary outcome of the Cochrane review was tumour size[1] and the outcome for the other SR was response rates as proportion of patients with a reduction in total volume of tumours to 50% or more compared to baseline and incidence of adverse events.[12]

In the cohort study, the primary outcome was size of reduction of cardiac rhabdomyoma in diameter and regression rate of tumour.[7] Two of the studies evaluate seizure frequency.[8,15] One study evaluated the renal angiomyolipoma response rate which was the proportion of patients with an angiomyolipoma response of a reduction in the sum of volumes of all target lesions of at least 50% compared to baseline, no new lesions greater than 1 cm in its longest diameter, no increase in kidney volume of at least 20% from the lowest value obtained from the patient, and no angiomyolipoma-related bleeding of grade 2 or more as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events.[14]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Both SRs were well conducted where the design was defined a priori and the search strategy was included and comprehensive.[1,12] There was duplicate study selection and data extraction for both by at least two investigators.[1,12] A grey literature search was included in the Cochrane review[1] and it is unclear if it was considered in the other SR.[12] Included studies were provided for both SRs but only the Cochrane review included the list of excluded studies.[1,12] The characteristics of the studies were included in both SRs but only the Cochrane review assessed the methodological quality of the included studies,[1] which wasn't included in the second SR.[12] Both SRs considered the quality of evidence when formulating the conclusions.[1,12] Heterogeneity was assessed in both SRs and the methods to combine the results was appropriate.[1,12] However, for the Yang et al. SR, the primary outcome was not defined beyond response rate in the pooling of the results and patients with different TSC indications were included. This review also pooled results from studies evaluating different drugs or formulations; therefore, it is unclear how the summary statistic might be interpreted in clinical settings.[12] Publication bias was included in the Cochrane review.[1] Conflict of interest was declared in both SRs.[1,12]

Four publications were identified that included two RCTs, one subgroup analysis of an RCT and one cohort study.[7,8,14,15] The objectives and methodology of all of the studies were well described and clear to follow but they all contained small sample sizes of less than 50 participants, with the exception of one RCT that included 366 patients, and a short duration of follow-up of up to one year, making it difficult to predict long term effectiveness and safety profile.[7,8,14,15] A power calculation was performed for both of the RCTs;[8,15] however, one of the studies did not enroll enough patients to meet the required target population.[15] It is possible that this is the reason the drug did not show a difference compared to placebo. All the RCTs were placebo-controlled, but it is difficult to determine how allocation concealment was maintained throughout the studies.[8,15] Results were presented in an organized manner for all of the studies and the appropriate statistical analysis were performed.[7,8,14,15] The subgroup analysis did not perform statistical testing between the treatment and placebo group, making it difficult to determine if there is a statistical difference between the intervention and comparator.[14] Of note, all of the identified publications that assessed everolimus were partly or completely funded by Novartis, the manufacturer of everolimus (Afinitor) who may have been involved in the study design and data analysis of the studies.[7,8,14] For the simolimus study,[15] the funding was from a research grant from the Dutch Epilepsy Foundation but some of the investigators disclosed they have received financial support from Novartis.

Summary of Findings

What is the clinical effectiveness of sirolimus for the treatment of tuberous sclerosis complex?

The Cochrane review included one study for sirolimus; however, it was the topical formulation and thus not relevant for this research question.[1] In the Yang et. al. SR, 10 of the 11 studies included sirolimus; however, four of them were the topical formulation.[12] All studies and interventions were pooled to demonstrate sirolimus or everolimus treatment had better response rates (not defined) compared with placebo with an odds ratio (OR) of 24.71 (95% confidence interval [CI] 7.46 to 81.72, p<0.001).[12] The included studies did not

report many adverse events but the most common ones include mouth ulceration, stomatitis, convulsion, acneiform rash, arthralgia, diarrhea, thrombocytopenia, hyperlipidemia, and lipoproteinemia.[12] No statistical analysis was performed for adverse events.[12]

One primary study was identified for sirolimus and was conducted in pediatric patients with TSC.[15] There was a 41% (95% CI -69% to 14%, p = 0.11) decrease in seizures in the patients who were on sirolimus but it was not statistically different from the placebo group.[15] However, this study did not enroll the target number of patients needed to reach statistical power. It is unclear if this affected the findings. In addition, all patients reported at least one adverse event, with the most common including upper respiratory tract infections (87%), gastrointestinal problems (83%), and acne-like skin lesions (74%).[15]

What is the clinical effectiveness of everolimus for the treatment of tuberous sclerosis complex?

The Cochrane review included two studies for everolimus and considered the outcomes of reduction in tumour size for both renal angiomyolipoma and SEGA.[1] The relative effect for everolimus for 50% reduction of renal angiomyolipoma compared with placebo was 24.7 (95% CI 3.5 to 173.4, p=0.001) and for 50% reduction of SEGA was 27.9 (95% CI 1.7 to 444.8, p=0.02) compared to placebo.[1] There was no difference for adverse events between the everolimus group and placebo group as the risk ratio was 1.07 (95% CI 0.9 to 1.2, p=0.24) but there were more adverse events in the everolimus group that resulted in dose reduction, interruption or withdrawal of the drug (risk ratio 3.14, 95% CI 1.82 to 5.42, p<0.0001).[1]

The other SR combined all studies that included sirolimus and everolimus together; however, only one study included considered everolimus.[12] Because the majority (10 of 11) studies examined sirolimus, the results are reported with the findings related to that treatment.

Three publications examining everolimus were identified and three different clinical manifestations of TSC were considered in the outcomes including reduction in rhabdomyoma, seizure frequency, and renal angiomyolipoma.[7,8,14]

One study by French et al. examined the reduction in seizure frequency and at 12 weeks, compared to baseline. The median percentage reduction in seizure frequency was 14.9% (95% CI 0.1 to 21.7), 29.3% (95% CI 18.8-41.9, p=0.0028 compared to placebo) and 39.6% (95% CI 35.0-48.7, p<0.0001 compared to placebo) in the placebo, low-exposure everolimus group and high-exposure everolimus group respectively.[8] The most common adverse events included stomatitis, diarrhea, nasopharyngitis, pyrexia and upper respiratory tract infection and occurred in both low- and high-exposure everolimus groups in at least 15% of the patients.[8]

One publication reported on the outcome of renal angiomyolipoma.[14] Kingswood et al.[14] was a subgroup analysis of the Franz et al.[6] study where patients who presented with renal angiomyolipoma were specifically evaluated. The group that received everolimus experienced a higher response rate of 53.3% (95% CI 34.3% to 71.7%) compared to those who received placebo with a response rate of 0.0% (95% CI 0.0% to 23.2%).[14] However, no statistical test was performed to determine statistical differences.[14] At 48 weeks of treatment, 80.0% of those receiving everolimus experienced at least 50% reduction of their renal angiomyolipoma.[14] The most commonly reported adverse events include mouth

ulceration, convulsion, stomatitis, fatigue and rash and these occurred in at least 20% of patients.[14]

Aw et al. conducted a cohort study where four neonates with TSC receiving everolimus were compared with ten historic controls with TSC and found all four neonates on treatment experienced at least a 50% reduction in the size of their rhabdomyoma while seven of ten who received similar reductions; however, no statistical testing was done to compare whether or not everolimus treatment was different from placebo.[7] It was noted the rhabdomyoma regression rate was 11.8 times faster for the everolimus group compared to historic control group but no statistical testing was performed.[7]

Limitations

The SRs and primary studies were generally well conducted; however, the evidence for the treatment of TSC remains to be limited to small studies with a short follow up. Many of the studies that were included in the SRs were non-randomized, which can introduce bias into the results. Additionally, one of the SRs pooled sirolimus and everolimus studies together and also included both oral and topical formulations without any subgroup analyses. It is difficult to generalize such results and to apply it in clinical settings when treating patients with TSC. No head-to-head trials comparing everolimus and sirolimus for the treatment of TSC were identified. Most of the available evidence examined everolimus; a single study considering sirolimus met the inclusion criteria for this review. While there have been some extension studies, these are non-comparative and are of lower quality evidence. Since these studies have small sample sizes, it is difficult to detect potential rare and serious adverse events that may be linked to the treatment of sirolimus and everolimus. Additionally, most studies report tumour size reduction and not clinically important outcomes for the patients. Considering the short duration of follow up for most studies, it is unclear if a reduction in tumour size correlates well with clinical outcomes.

Conclusions and Implications for Decision or Policy Making

A total of eight relevant publications were identified, including two systematic reviews,[1,12] two RCTs,[8,15] a subgroup analysis of an RCT,[14] and one cohort study.[7] Two additional systematic reviews[11,13] were identified but neither included controlled studies with comparisons of interest for this review.

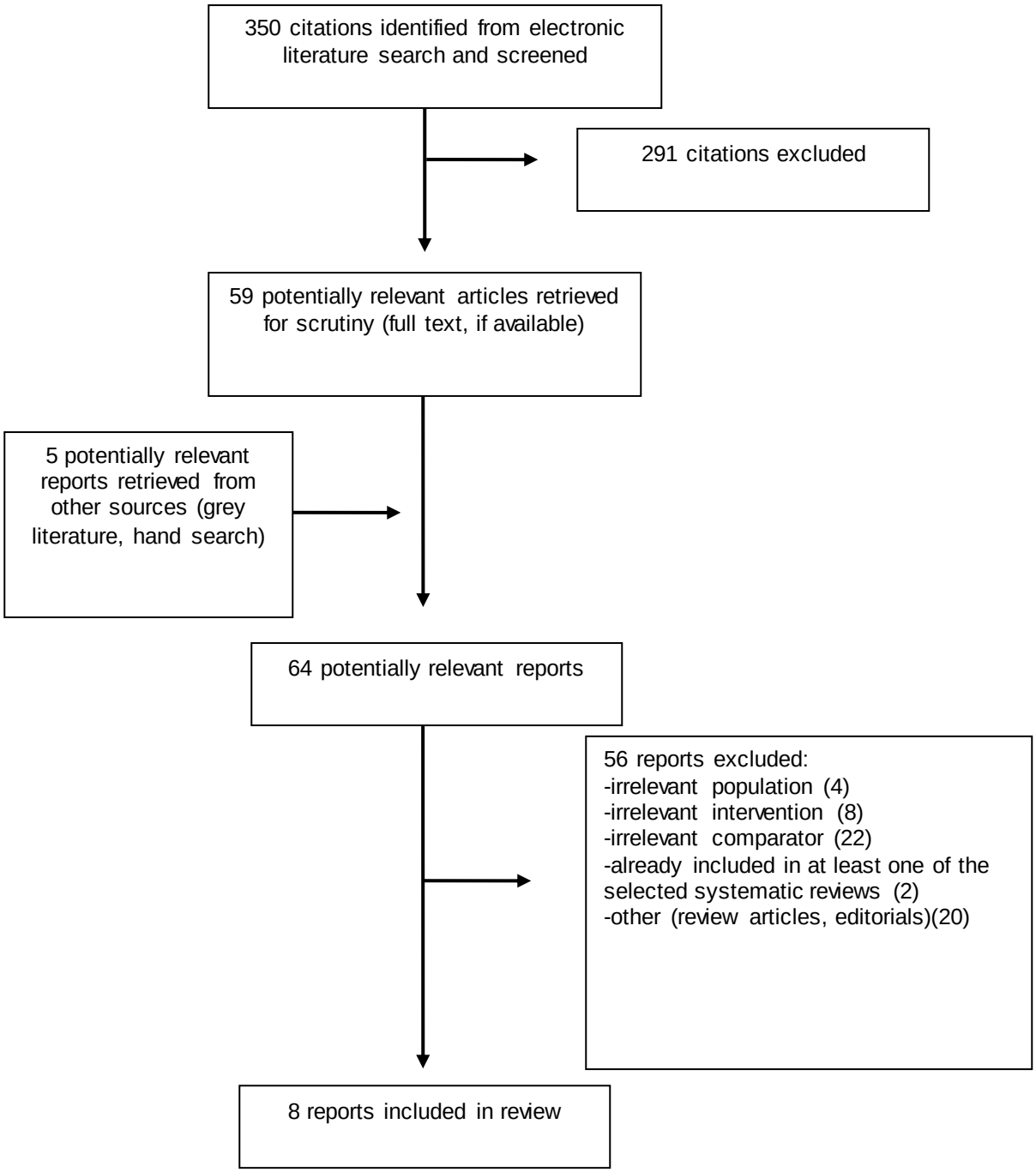
Since the CDEC recommendations in 2013 and 2015,[4,5] additional investigations have been published regarding the use of everolimus compared to sirolimus in the management of TSC associated manifestations including seizures, rhabdomyolipoma, and renal angiomyolipoma. The evidence suggests that treatment with everolimus or sirolimus demonstrated a better response rate when compared to placebo for various symptoms of TSC. The most commonly reported adverse events align with the known adverse events of these agents including stomatitis, nasopharynitis, and upper respiratory tract infections. However, some of these adverse events have resulted in discontinuations or dose reductions. Given the short duration of studies the long term effectiveness and safety remains unclear based on available evidence. There remains a lack of evidence that compares sirolimus to everolimus for the treatment of TSC-associated manifestations.

References

1. Sasongko TH, Ismail NF, Zabidi-Hussin Z. Rapamycin and rapalogs for tuberous sclerosis complex. Cochrane Database Syst Rev. 2016 Jul 13;7:CD011272.
2. Owens J, Bodensteiner JB, . Tuberous sclerosis complex: genetics,clinical features, and diagnosis. In: Post TW, editor. UpToDate [Internet]. Waltham (MA): UpToDate; 2017 Sep 1 [cited 2017 Nov 16]. Available from: www.uptodate.com Subscription required.
3. Bodensteiner JB, Randle S. Tuberous sclerosis complex: management and prognosis. In: Post TW, editor. UpToDate [Internet]. Waltham (MA): UpToDate; 2017 Sep 1 [cited 2017 Nov 16]. Available from: www.uptodate.com Subscription required.
4. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: everolimus (Afinitor - Novartis Pharmaceuticals Canada) [Internet]. Ottawa (ON): CADTH; 2013 Sep 25. [cited 2017 Nov 16]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/cdr_compete_Afinitor_September_27_13.pdf
5. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: everolimus (Afinitor - Novartis Pharmaceuticals Canada Inc.) [Internet]. Ottawa (ON): CADTH; 2015 Apr 15. [cited 2017 Nov 16]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/cdr_compelte_SR0376_Afinitor_Apr-17-15.pdf
6. Franz DN, Belousova E, Sparagana S, Bebin EM, Frost M, Kuperman R, et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet. 2013 Jan 12;381(9861):125-32.
7. Aw F, Goyer I, Raboisson MJ, Boutin C, Major P, Dahdah N. Accelerated cardiac rhabdomyoma regression with everolimus in infants with tuberous sclerosis complex. Pediatr Cardiol. 2017 Feb;38(2):394-400.
8. French JA, Lawson JA, Yapici Z, Ikeda H, Polster T, Nabbout R, et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. Lancet. 2016 Oct 29;388(10056):2153-63.
9. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007 [cited 2017 Nov 16];7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf
10. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2017 Nov 16];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf
11. Sasongko TH, Ismail NF, Nik Abdul Malik NM, Zabidi-Hussin ZA. Rapamycin and its analogues (rapalogs) for tuberous sclerosis complex-associated tumors: a systematic review on non-randomized studies using meta-analysis. Orphanet J Rare Dis [Internet]. 2015 Aug 12 [cited 2017 Oct 27];10:95. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4531483
12. Yang G, Yang L, Yang X, Shi X, Wang J, Liu Y, et al. Efficacy and safety of a mammalian target of rapamycin inhibitor in pediatric patients with tuberous sclerosis complex: A systematic review and meta-analysis. Exp Ther Med [Internet]. 2015 Feb [cited 2017 Oct 27];9(2):626-30. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4280930
13. Peng ZF, Yang L, Wang TT, Han P, Liu ZH, Wei Q. Efficacy and safety of sirolimus for renal angiomyolipoma in patients with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis: a systematic review. J Urol. 2014 Nov;192(5):1424-30.
14. Kingswood JC, Jozwiak S, Belousova ED, Frost MD, Kuperman RA, Bebin EM, et al. The effect of everolimus on renal angiomyolipoma in patients with tuberous sclerosis complex being treated for subependymal giant cell astrocytoma: subgroup results from the randomized, placebo-controlled, Phase 3 trial EXIST-1. Nephrol Dial Transplant [Internet]. 2014 Jun [cited 2017 Oct 27];29(6):1203-10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4852219

15. Overwater IE, Rietman AB, Bindels-de HK, Looman CW, Rizopoulos D, Sibindi TM, et al. Sirolimus for epilepsy in children with tuberous sclerosis complex: A randomized controlled trial. Neurology. 2016 Sep 6;87(10):1011-8.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 1: Characteristics of Systematic Reviews

First Author, Publication Year	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Sasongko et al. 2016[1]	Randomized or quasi-randomized studies 3 studies were included for a total of 263 patients Two studies studied everolimus and one study studied topical sirolimus	Adults with known TSC proven by clinical features	rapamycin or rapalogs designed to reduce any TSC-associated symptoms in people with TSC	Placebo or any standard treatments given systemically or topically	Primary outcome: tumour size Secondary outcome: skin lesion response, aneurysm size for angiomyolipomas, frequency of seizures, forced FEV_1/FVC ratio, creatinine level, any reported adverse effect or toxicity
Yang et al. 2015[12]	11 studies including RCTs, case series or case reports for a total of 129 pediatric patients were included: - 5 case reports - 5 case series - 1 RCT One study evaluated everolimus and the rest considered sirolimus	Age range from 1.0 years to 18.0 years Must have TSC	Any mTOR inhibitor therapy including rapapmycin, sirolimus and everolimus	Placebo or pretreatment status	Response rates to TSC manifestations and incidence of adverse events Length of follow-up range: 3 months to 16 months

CADTH = Canadian Agency for Drugs and Technologies in Health; FEV_1 = forced expiratory volume at one second; FVC = forced vital capacity; mTOR = mammalian target of rapamycin; RCT = randomized controlled trial; SEGA = subependymal giant cell astrocytoma; TSC = tuberous sclerosis

Table 2: Overlap in Included Studies between Systematic Reviews with Relevant Primary Studies

Study author (year of publication)	Systematic Reviews	
	Sasongko et al. 2016[1]	Yang et al. 2015[12]
Franz (2006)		✓
Hofbauer (2008)		✓
Birca (2010)		✓

Study author (year of publication)	Systematic Reviews	
	Sasongko et al. 2016[1]	Yang et al. 2015[12]
Lam (2010)		✓
Wataya-Kaneda (2011)		✓
Pressey (2010)		✓
Sparagana (2010)		✓
Foster (2012)		✓
Koenig (2012)	✓	
Salido (2012)		✓
Stachler (2012)		✓
Franz (2013)	✓	✓
Bissler (2013)	✓	

Table 3: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design, N	Population Characteristics	Intervention	Comparator(s)	Outcomes of Interest
Aw et al. 2017[7] Canada	Cohort N = 4	Four neonates with TSC with cardiac rhabdomyoma were compared to 10 historic controls with a median follow-up of 53 months	Everolimus dosed at 4.5 mg/m^2/week (0.1 mg per daily dose)	Historic controls who received no treatment	Size reduction of rhabdomyoma and regression rate of tumour
Overwater et al. 2016[15] the Netherlands	Randomized, placebo-controlled crossover trial N = 23	Children between 3 months and 12 years old with definite clinical diagnosis of TSC and at least 1 epileptic seizure per week & resistant to at least 2 AEDs Age range = 1.8 to 10.9 years 11/23 male	1 mg/ml sirolimus oral solution titrated to C_{min} = 5-10 ng/mL for 6 months add on to current AED regimen	Placebo	Seizure frequency assessed by daily seizure diary
French et al. 2016[8] 25 Countries	Double blind, RCT N = 366	Patients aged 2 to 65 with confirmed diagnosis of TSC & treatment-resistant epilepsy with ≥ 16 seizures during the 8-week baseline phase Median age (range) = 10.1 years (2.2-56.3) 51.9% male	Everolimus titrated to C_{min} = 3-7 ng/mL (low exposure) Everolimus titrated to C_{min} = 9-15 ng/mL (high exposure)	Placebo	Reduction in seizure frequency an median percentage reduction in seizure frequency after 12 weeks of maintenance period

First Author, Publication Year, Country	Study Design, N	Population Characteristics	Intervention	Comparator(s)	Outcomes of Interest
Kingswood et al. 2014[14] 10 countries	Double-blind, randomized, multi-center, placebo controlled trial (subgroup analysis) N = 44	Patients with TSC with at one of more angiomyolipomata that were ≥ 1.0 cm in longest diameter and with renal angiomyolipoma Age range = 4.5 to 23.9 years old	Everolimus	Placebo	Angiomyolipoma response rate based on proportion of patients with confirmed angiomyolipoma response

AED = antiepileptic drugs; CADTH = Canadian Agency for Drugs and Technologies in Health; C_{min} = target trough concentration; RCT = randomized controlled trial; SEGA = subependymal giant cell astrocytoma; TSC = tuberous sclerosis complex;

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[9]

AMSTAR Item		Sasongko et al. 2016[1]	Yang et al. 2015[12]
Was an a priori design provided?		+	+
Was there duplicate study selection and data extraction?	Selection	+	+
	Extraction	+	+
Was a comprehensive literature search performed?		+	+
Was the status of publication (i.e. grey literature) used as an inclusion criteria?		+	?
Was a list of studies (included and excluded) provided?	Included	+	+
	Excluded	+	-
Were the characteristics of the included studies provided?		+	+
Was the scientific quality of the included studies assessed and documented?		+	-
Was the scientific quality of included studies used appropriately in formulating conclusion?		+	+
Were the methods used to combine the findings of studies appropriate?		+	+
Was the likelihood of publication bias assessed?		+	-
Was conflict of interest included?		+	+

Legend: + = Yes, X = No, ? = Unclear

Table 5: Strengths and Limitations of Randomized Controlled Trials using Downs and Black[10]

Strengths	Limitations
Aw et al. 2017[7]	
• Objectives and outcome measures were clearly stated. • Methods were clear and easy to understand. • Primary outcomes were well described and results were easy to understand. • At baseline, the median size of the rhabdomyoma was comparable between groups. • Adverse effects were documented.	• Non-randomized cohort study. • Small population, specifically in neonates. • No statistical analysis was done for reduction in size of rhabdomyoma although it was listed as one of the primary outcomes. • Short duration of follow-up (median of 53 months). • Unclear about long-term adverse effects. • Partially funded by Novartis.

Strengths	Limitations
Overwater et al. 2016[15]	
• Clearly stated the objectives and methods. • Statistical analysis appears to be correct, chose to use intention-to-treat analysis. • Primary and secondary outcomes are objective measures. • Cross over design can minimize confounder effects because each patient was their own control. • Results were described clearly for both primary and secondary outcomes. • Adverse events were clearly documented.	• Short term study (6 months, then crossover 6 months) • Power calculation was completed; however, the enrollment did not reach the required numbers. • Overall small population, it would be difficult to detect rare adverse events. • Patients' background AED regimen was changing through the study, it is difficult to determine how much of it affected the results. • Unclear long term efficacy and safety. • Study is funded by the Dutch Epilepsy Foundation; authors have disclosed their conflict of interests which includes non-financial support from Novartis.
French et al. 2016[8]	
• Clearly stated the objectives and the outcomes of interest in the methods for the study. • The intervention and comparisons are clearly described. • 90% power calculation was done. • Intention to treat analysis was done. • Power calculation was done to determine appropriate sample size. • Appropriately recruited participants from the population of interest. • 1:1:1 block randomization was done based on age groups. • The trial was blinded from the patients, investigators, site personnel and sponsor's study team. • Statistics that were used appears to be appropriate. • Similar rates of drop-out between the groups. • Results are presented in an organized manner in text and in the tables.	• Short term study (12 weeks). • Blinding was not concealed from those in charge of drug supply, implementation of randomization list, and pharmacokinetic analyses. • Patients used other anti-epileptic medications concurrently with varying proportions at baseline between the three groups. • 18% of study population was over 18 years old. • Funding is from Novartis Pharmaceuticals Corporation.
Kingswood et al. 2014[14]	
• The objectives were clearly stated. • Primary endpoint was clearly defined. • Adverse events were reported in detail. • Baseline characteristics appear to be well balanced except for more males in the everolimus group. • Approximately 2:1 randomization for everolimus treatment and placebo treatment. • Similar dropout rates were noted between the two groups.	• Full details for methods is published elsewhere and not presented in detail. • Small population of 44. • Duration was only for 48 weeks. • No statistical testing was performed for the efficacy endpoints. • This is a subgroup analysis, which suggests that the study was not designed *a priori* for this particular population and outcome. • A number of the investigators reported conflict of interests with various companies, including Novartis.

AED = antiepileptic drugs; CADTH = Canadian Agency for Drugs and Technologies in Health; C_{min} = target trough concentration; TSC = tuberous sclerosis complex;

Appendix 4: Main Study Findings and Author's Conclusions

Table 6: Summary of Findings of Systematic Reviews

Main Study Findings	Author's Conclusion
Sasongko et al. 2016[1]	
• For the outcome of 50% reduction in tumour size for renal angiomyolipoma, comparing oral everolimus to placebo, the relative effect was 24.7 (95% CI 3.5 to 173.4, p = 0.001) based on two studies. • For the outcome of 50% reduction in tumour size of subependymal giant cell astrocytoma (SEGA), comparing oral everolimus to placebo, the relative effect was 27.9 (95% CI 1.7 to 444.8, p = 0.02), based on 1 study. • The relative effect for the response to skin lesions comparing oral everolimus to placebo was 5.8 (95% CI 2.3 to 14.5, p = 0.0002) based on two studies. • There appears to be no difference between the oral everolimus group and placebo for any adverse events and the relative effect was 1.07 (95% CI 0.9 to 1.2, p=0.24). However, there were more adverse events that lead to dose reduction, interruption or withdrawal in the oral everolimus group with a relative effect of 3.14 (95% CI 1.8 to 5.4, p<0.0001).	*"Convincing evidence of a reduction of tumour size after 24 weeks of treatment with oral everolimus (rapalogs) in both renal angiomyolipoma and SEGA would provide sufficient evidence for its use in clinical practice as the benefits outweigh the risks. With this in mind, and with the positive effects on the size reduction in renal angiomyolipoma and SEGA, this review concurs with the decision of the U.S. Food and Drug Administration (FDA) and European Medicine Agency (EMA) on the use of everolimus for both types of tumours. Rapamycin or rapalogs may also have a beneficial effect on skin lesions."* (p. 23)[1]
Yang et al. 2015[12]	
• The response rate for those treated with mTOR inhibitor therapy compared with those treated with non-mTOR inhibitor therapy was calculated to be odds ratio 24.71 (95% CI 7.46 to 81.72, p<0.001). • Most common adverse events associated with mTOR therapy included mouth ulceration, stomatitis, convulsion, acneiform rash, arthralgia, diarrhea, thrombocytopenia, hyperlipidemia, and lipoproteinemia. No statistical analysis was performed for adverse events because most studies reported very few adverse effects.	*"The results of the study suggest that mTOR inhibitor therapy can increase clinical response rates compared with non-mTOR inhibitor therapy. This is the first systematic review investigating the efficacy and safety of mTOR therapy for the treatment of pediatric patients with TSC. Our findings are in agreement with a recently published RCT".* (p. 629)[12]

Table 7: Summary of Findings of Clinical Effectiveness Studies

Main Study Findings	Author's Conclusion
Aw et al. 2016[7]	
• All four cases treated with everolimus experienced at least 50% size reduction of rhabdomyoma while 7 of 10 controls experienced 50% size reduction and the rest experienced 20% to 30% size reduction of their rhabdomyoma. No statistical analysis was done to compare between the two groups for treatment effect. • Rhabdomyoma regression rate was 11.8 times faster in the group treated with everolimus compared to historic controls (p<0.001).	*"This study demonstrates that everolimus is efficacious for the size reduction of RHM during the neonatal period, but this approach should be used with caution, only in selective cases, because long-term effects remain unknown."* (p. 399)[7]

Main Study Findings	Author's Conclusion
Overwater et al. 2016[15]	
• There was a 41% decrease in seizures with the use of sirolimus (95% CI – 69% to 14%, p=0.11) for the 23 children with TSC. • All patients reported at least 1 adverse event including upper respiratory tract infections, gastrointestinal problems, and acne-like skin lesions. Five patients discontinued sirolimus due to adverse events.	*"We were unable to show a significant effect of sirolimus on seizure reduction in children with TSC and intractable epilepsy. A beneficial effect is not ruled out, however, and further studies are needed to assess the value of mTORC1 inhibitors in the treatment of TSC-related epilepsy."* (p.1017)[15]
French et al. 2016[8]	
• Comparing week 12 with baseline, the median percentage reduction in seizure frequency was 14.9% • The most common adverse event that occurred in more than 15% of patients in either everolimus treatment group included stomatitis, diarrhea, nasopharyngitis, pyrexia and upper respiratory tract infection.	*"In conclusion, our findings demonstrate that everolimus treatment of mixed-type seizures in patients with tuberous sclerosis complex, despite the high baseline burden of seizures in these individuals, can lead to a clinically meaningful reduction in seizure frequency with a favourable benefit–risk ratio that improves with ongoing treatment."* (p. 2161)[8]
Kingswood et al. 2014[14]	
• Those treated with everolimus had a higher angiomyolipoma response rate 53.3% (95% CI 34.3% to 71.7%) compared to those treated with placebo 0.0% (95% CI 0.0% to 23.2%). No statistical test was reported to determine the statistical differences. • Only patients receiving everolimus achieved ≥ 50% reduction of their angiomyolipoma with 56.5%, 78.3% and 80.0% achieving such reductions at 12, 24 and 48 weeks respectively. • The most common adverse events include mouth ulceration, convulsion, stomatitis, fatigue and rash, which were reported in ≥ 20% of patients.	*"This trial has shown that everolimus is effective in reducing angiomyolipoma lesion volume in patients with SEGA associated with TSC who also presented with angiomyolipoma."* (p.1210)[14] *"Everolimus represents a pharmacological treatment option for patients with TSC who have SEGA and concomitant angiomyolipoma."* (p.1210)[14]