

EVEROLIMUS FOR SUBEPENDYMAL GIANT CELL ASTROCYTOMAS ASSOCIATED WITH TUBEROUS SCLEROSIS COMPLEX

QUESTIONS TO BE ADDRESSED:

1. Is Everolimus clinically effective in reduction in SEGA tumour volumes and improvement of quality of life in patients with the Tuberous Sclerosis complex compared with no intervention or with other standardised treatments?
2. Is Everolimus cost effective in patients suffering from SEGA associated with TSC?

SUMMARY:

Background

- Tuberous sclerosis complex (TSC) is a rare genetic disorder that causes the development of benign tumours in multiple organs.
- Subependymal giant cell astrocytomas (SEGAs) are brain tumours that are almost exclusively related to TSC and develop in up to 20% of TSC patients.
- They are usually slow growing, but can ultimately lead to increased intracranial pressure and hydrocephalus.
- Surgery is the standard treatment, however due to the deep location of SEGAs they can be difficult to resect, leading to complications or incomplete clearance.
- A pharmacological alternative, everolimus (a mammalian target of rapamycin inhibitor), is licensed for the treatment of SEGAs in TSC patients who are not amenable to surgery.

Clinical Effectiveness

- One well-conducted randomised controlled trial (EXIST-1) was found that looked at the effectiveness of everolimus compared to placebo in 117 TSC patients with SEGA progression who were unlikely to require surgery.
- The trial showed that everolimus was effective at reducing SEGA volume compared to placebo after a median follow-up of 10 months.
- 35% of patients in the everolimus arm had at least a 50% reduction in SEGA volume compared to 0% in the placebo arm. No cases of progression of SEGA were seen in the everolimus group compared to 15% in the placebo arm.
- The long-term effectiveness of everolimus is uncertain, as all participants in the placebo arm were crossed-over to everolimus at the end of the trial.
- Although uncertain, the uncontrolled extension phase of EXIST-1 showed that the short-term benefits of everolimus were generally maintained after a median follow-up of 28 months.
- No studies were found comparing everolimus to other treatments.

Cost Effectiveness

- No studies were found assessing the cost-effectiveness of everolimus in patients with SEGA associated with TSC.

Safety

- In EXIST-1, adverse events were common and mostly not serious.

- The most commonly reported adverse events were mouth ulceration and stomatitis, both of which were experienced by around a third of all everolimus patients in EXIST-1.
- Half of the everolimus patients temporarily stopped treatment or had their doses reduced due to adverse events, but no patient discontinued treatment because of adverse events during the period of randomisation.
- In the uncontrolled follow-up period treatment was discontinued in 5% due to an adverse event attributed to everolimus.

1 Context

1.1 Introduction

Tuberous sclerosis complex (TSC) is a rare genetic disorder which is characterised by the development of multiple benign tumours (hamartomas) mainly in the brain, kidney, liver, skin, heart and lung. It is caused by autosomal dominant mutations in TSC1 or TSC2 tumour suppressor genes, resulting in increased activation of the mammalian target of rapamycin (mTOR), a major cell growth and proliferation controller. Symptoms can include hydrocephalus, epilepsy, behavioural problems, learning disabilities, renal dysfunction, breathing difficulties and skin malformations. Up to 90% of individuals with TSC have epilepsy, up to 80% develop angiomyolipoma and around a half to two thirds have developmental delays ranging from mild learning disabilities to severe impairment.^{1, 2}

Subependymal giant cell astrocytomas (SEGAs) are benign, slow-growing, brain tumours that are almost exclusively associated with TSC and develop in 5-20% of TSC patients usually during childhood and adolescence.³ They can be solitary or multiple and usually form within the ventricles near the foramen of monro, an opening deep in the brain that drains cerebrospinal fluid. They are usually asymptomatic until they grow large enough to block circulation of the cerebrospinal fluid (CSF), leading to hydrocephalus. Common symptoms of SEGA include headaches, nausea, vomiting, seizures, behavioural changes, and visual problems. Typically, serial neuroimaging for SEGA is performed even in the absence of symptoms every one to three years in children with TSC until they reach their mid-20s. Surgical resection has been the standard treatment, but the deep location of SEGAs can make resection difficult and there is a risk of perioperative complications or incomplete clearance. An alternative is pharmacological treatment with everolimus, an mTOR inhibitor that can shrink or stabilise tumours.⁴

1.2 Existing national policies and guidance

We found no national policies or guidance on everolimus for the treatment of SEGA associated with TSC. We found international guidelines on the diagnosis, screening and treatment (including everolimus) of SEGAs.⁵ These are based on recommendations made by a panel of experts at the international TSC consensus conference held in 2012. They concluded that “treatment decisions should be balanced and should be based on multiple factors that are unique to the individual TSC patient, including his or her clinical condition, anatomic considerations specific to the SEGA, surgeon experience, experience of the centre with using mTOR inhibitor, prior history of SEGA resection, other TSC related comorbidities, and patient/parental preference”.

2 Epidemiology

In the UK, the estimated prevalence of TSC is 8.8 per 100,000 population. This equates to around 5,680 individuals living with TSC in the UK. Assuming SEGA occurs in 5-20% of individuals with TSC, an estimated 284 to 1,136 individuals will have SEGA associated with TSC in the UK.⁶ However this is likely to be an underestimation of the true prevalence, because diagnosis depends on clinical features that are variable and prevalence is increasing with better identification of less severe cases.

3 The intervention

Everolimus (Votubia) is an mTOR inhibitor derived from sirolimus (rapamycin), a macrolide antibiotic. It acts by binding to the intracellular immunophilin FKBP-12 to form a complex which inhibits mTOR (a major cell growth and proliferation controller), which is overactivated in individuals with TSC.²

Everolimus was approved by United States Food and Drug Administration and the European Medicines Agency in 2010 and 2011 respectively for the treatment of patients aged 3 years and older with SEGA associated with TSC who require therapeutic intervention but are not amenable to surgery. This has now been expanded to include children under 3 years old. Everolimus is also approved for adults with renal angiomyolipoma and TSC not requiring immediate surgery.^{7,8}

Everolimus is taken as a tablet once daily and the recommended starting dose for the treatment of patients with SEGA is 4.5 mg/m². Doses that will be tolerated and effective vary between patients and titration may be required to obtain the optimal therapeutic effect. Dosing is individualised based on body surface area and whether antiepileptic medication is also being taken.

4 Findings

A literature search was performed on the 5th of August 2015 for everolimus and SEGA associated with TSC. The search was run on PubMed, Embase, Cochrane Library, TRIP and NICE Evidence Search, and was limited to English language results from 2005 onwards.

No systematic reviews or meta-analyses for everolimus and SEGA associated with TSC were found.

We found one randomised controlled trial (RCT).⁹ This trial (EXIST-1) compared everolimus to placebo in individuals with SEGA associated with TSC. In addition to the main EXIST-1 results, we found four papers reporting on this RCT – one paper on an uncontrolled extension of the trial,¹⁰ a sub-group analysis looking at participants with renal angiomyolipoma,¹¹ a sub-group analysis looking at TSC mutation type effects,¹² and a case series on children aged 3 years and under with epilepsy who had been randomised to everolimus in the EXIST-1 trial from a centre in Poland.¹³

No RCTs were found looking at the effectiveness of everolimus compared to other mTOR inhibitors or to surgery.

Three papers reporting on two case series looking at the effectiveness or safety of everolimus in individuals with SEGA associated with TSC were also included.^{14,15,16}

Abstracts, conference papers and case reports were excluded, as these are not detailed enough for critical appraisal.

No studies evaluating the cost-effectiveness of everolimus for the treatment of SEGA associated with TSC were found.

The search strategy used is detailed in section 7, and a detailed summary of the studies included in this review can be found in Table 1.

4.1 Evidence of effectiveness

EXIST-1 Franz et al 2013⁹

This is a randomised, double blind trial comparing the effectiveness of everolimus to placebo in patients with SEGA associated with TSC in 24 international centres. Patients were randomised in a 2:1 ratio to oral everolimus 4.5mg/m² per day (titrated to achieve blood trough concentrations of 5-15ng/ml) or placebo. Eligible patients had a definite diagnosis of TSC and at least one SEGA lesion of 1cm or greater and either serial radiological evidence of SEGA growth, presence of a new SEGA lesion of 1cm or greater, or new or worsening hydrocephalus. The primary outcome was the proportion of patients with SEGA response (defined as a reduction in the total volume of all target SEGA of 50% or more relative to baseline), in the absence of worsening of non-target SEGA, new lesions of 1cm or greater in diameter, and worsening hydrocephalus. The analysis was stratified by use of enzyme-inducing antiepileptic drugs at randomisation, sex and age. Brain MRI was carried out at 3, 6 and 12 months after starting treatment and then yearly thereafter. Secondary outcomes included time to SEGA progression, absolute change in frequency of total seizure events per 24-hour EEG from baseline to week 24, angiomyolipoma response, and skin lesion response. SEGA progression was defined as an increase of 25% or more from the nadir volume at baseline, unequivocal worsening of non-target lesions of SEGA, the appearance of new lesions of 1cm or more in diameter, or worsening hydrocephalus. The data cut-off date for all analyses was 6 months after the last patient was randomised.

A total of 117 patients were randomised, 78 to everolimus and 39 to placebo. At baseline, the median age of the population was 9.5 years, 94% of patients had skin lesions present and 7% had a history of surgery related to their SEGA. The median duration of study treatment was 41.9 weeks (range 24.0 to 78.9) for individuals in the everolimus arm and 36.1 weeks (range 13.9 to 79.7) for those in the placebo arm. The median dose intensity of everolimus was 5.9 mg/m² per day (range 2.3 to 11.8). At data cut-off, results showed that everolimus was superior to placebo for SEGA response with 35% of patients (n=27/78) in the everolimus arm showing a reduction in the total volume of SEGA by 50% or more compared with 0% of patients (n=0/39) in the placebo arm. This was a statistically significant difference of 35% (95% CI = 15 to 52, p<0.0001). The subgroup analyses were not adequately powered to detect differences in effect size by antiepileptic drug use, sex or age. Time to SEGA response was not reported.

Progression was observed in 6 patients in the placebo arm (15%) and none in the everolimus arm. The authors estimated progression-free rates at 6 months were 100% for the everolimus arm and 85.7% for the placebo arm (p=0.0002). The results on seizures were inconclusive as only around a third of patients had evidence of suffering seizures at baseline so the sample size was too small to detect significant changes.

Everolimus was seen to have additional benefits on skin lesions and angiomyolipoma with 53% (n=16/30) in the everolimus group versus none (n=0/14) in the placebo group having an angiomyolipoma response and 42% (n=30/72) in the everolimus arm vs 11% (4/38) in the placebo arm having a skin lesion response (p=0.0004). No confidence intervals were reported.

Results were analysed on an intention to treat basis. After a median follow-up of 9.7 months, 10 out of 117 patients (2 in the everolimus arm and 8 in the placebo arm) had discontinued treatment. Within the placebo arm, the majority (6 patients) discontinued treatment due to disease progression. These patients had their treatment changed to everolimus and their data were censored at that point. Within the everolimus arm, one patient was lost to follow-up and one withdrew consent.

Adverse events are detailed in the safety section below.

This study was generally well-conducted with objectives, eligibility criteria, and results clearly stated, and appropriate statistical analyses carried out. Patients were randomised using an interactive internet-response system. No further details of the randomisation process were given, but there is no reason to suspect that it was not done adequately as the baseline patient characteristics are generally well balanced, with the exception of sex and presence of hydrocephalus. The everolimus arm had a higher proportion of males (63% compared to 46% in the placebo arm) and a higher proportion of patients with the presence of hydrocephalus at baseline (10% compared to 0% in the placebo arm). There is no apparent reason why these differences would have introduced bias. The trial appears to be adequately blinded with outcome assessors being blinded as well as patients and health professionals. One problem with the trial design is that all patients in the placebo arm were given the option of starting everolimus at 6 months after the last patient was randomised, which makes it impossible to assess the long-term effectiveness of everolimus. Given that everolimus is likely to be taken long-term this is a major flaw. A further issue is that it is not clear if a reduction in SEGA of 50% is clinically significant. It would have been useful to have also included change in volume of SEGA as an outcome. Furthermore, the aim of treatment of SEGAs is to prevent hydrocephalus and the number of new or worsening cases of hydrocephalus were not reported. It is clear that there were no cases in the everolimus arm as no progressions were observed, but it is not known how many, if any cases were seen in the placebo arm. Quality of life was not measured.

The EXIST-1 trial was funded by Novartis Pharmaceuticals, the maker of everolimus, and the majority of authors were reported to be either employees of Novartis, consultants for Novartis or received travel payments, research funding or speaker honoraria from Novartis.

Open-label extension of EXIST-1 Franz et al 2014¹⁰

This is an interim analysis of an open-labelled, uncontrolled extension of the EXIST-1 trial described above. The analysis includes cumulative data from patients who were treated with at least one dose of everolimus from both the core and extension phase of the trial. A total of 111 patients were included, 78 of which were initially randomised to everolimus and 33 patients crossed-over from placebo to everolimus either during the core phase of the trial or at the beginning of the extension phase. Six patients (5%) in the original placebo group did not enter the extension phase due to either compliant issues (n=2), withdrawing consent (n=2), having stable disease (n=1) or entering another trial (n=1). The median duration of everolimus exposure was 29.3 months (range = 1.9 to 40.5) and the median follow-up time was 28.3 months (range = 1.9 to 38.8). The median dose intensity of everolimus was 5.9mg/m² per day (range = 1.0 to 13.7).

At data cut-off, a 50% or greater SEGA reduction (SEGA response) had been achieved in 54 out of 111 patients (49% (95% CI = 39 to 58%)). The median time to SEGA response was 3.58 months (IQR = 2.83 to 5.65). SEGA response was achieved by 27% at week 12, 37% at week 24, 46% at week 48, 47% at week 96 and 38% at week 144. 95% confidence intervals were not reported for these time points. The median reduction in SEGA volume was 0.57cm³ (IQR = 0.23 to 1.02) at week 12 and didn't appear to change significantly over time. Sub-group analyses for age, sex and TSC mutation were reported, but these are unlikely to be reliable due to the small sample sizes involved. Nine patients (8%) had SEGA progression. The authors report that progression occurred in the majority of these patients due to treatment being stopped or everolimus blood concentrations being markedly reduced. Only one patient underwent surgery during the study and this was a patient who developed hydrocephalus in the absence of SEGA growth. Sixteen patients (14%) discontinued treatment either due to adverse events (n=6), administrative problems (n=3), lost to follow-up (n=3), withdrawing consent (n=2), disease progression (n=1) or surgical intervention (n=1).

Adverse events are reported in the safety section below.

The extension phase was uncontrolled and therefore of relatively limited value in establishing clinical efficacy compared to the value of a randomised blind study. While it does appear that much of the benefit shown in the first 6 months of treatment of everolimus is maintained at around 3 years, the absence of a control group means that it is impossible to quantify the effects of everolimus on avoiding complications and the need for the surgery.

Sub-group analysis of EXIST-1 (patients with angiomyolipoma) Kingswood et al 2014¹¹

This is a sub-group analysis of the EXIST-1 trial looking at participants with renal angiomyolipoma at baseline. In total, 44 patients were included in the sub-group analysis, 30 of which received everolimus and 14 received placebo. The baseline characteristics were well balanced between the two groups with the exception of gender, but this was considered not to be clinically significant. The angiomyolipoma response rate was 53.3% (95% CI = 34.3 to 71.7%) in the everolimus arm compared to 0% (95% CI = 0 to 23.2%) in the placebo arm. The response rate difference is statistically significant because the confidence intervals don't overlap, but confidence intervals and a p-value are not reported for response difference. Response rates were reported at week 12, 24 and 48, but it is impossible to draw meaningful conclusions from these results due to the small numbers involved.

Sub-group analysis of EXIST-1 (TSC mutation type and location) Kwiatowski et al 2015¹²

This is a sub-group analysis of EXIST-1 which looks at the effects of TSC mutation type and location on SEGA response to everolimus. DNA samples from 116 patients out of the 117 patients randomised in EXIST-1 were available for mutation analysis. Thirteen patients (11.2%) had mutations in TSC1 (10 in everolimus arm and 3 in placebo arm), 84 patients (72.4%) had mutations in TSC2 (55 in the everolimus arm and 29 in the placebo arm) and 19 patients (16.4%) had no mutation identified (12 in the everolimus arm and 7 in the placebo arm). The authors reported that the proportion of TSC1 mutations in EXIST-1 was lower than seen in other SEGA series.

Numerical results were not reported, only a series of graphs showing SEGA response by TSC gene mutation. The authors concluded that there was no apparent association between mutation type or location within each gene and response to everolimus. However these conclusions were based on small numbers (e.g. only 3 patients in the placebo arm had mutations in TSC1) and should therefore be treated with caution.

The following three case series were found.

Kotulska et al 2013¹³

This paper describes the results of eight children aged 3 years and under who were enrolled into EXIST-1 trial from a centre in Warsaw, Poland. The participants were all randomised to everolimus and had a history of epilepsy. These results do not add any further information to the main results of EXIST-1.

Krueger et al 2010¹⁴ & 2013¹⁵

These papers report on a case series of 28 patients with SEGA associated with TSC who were treated with everolimus for a minimum of 6 months. Kreuger et al 2010 reports the short-term effects (up to 6 months) and Kreuger et al 2013 reports on the long-term effects (up to 3 years). In addition to SEGA response they also assess effects on seizures, quality of life, and neurocognition.

At 6 months, the findings were similar to those in EXIST-1 with a $\geq 50\%$ reduction in SEGA volume achieved by around a third of patients (32% (n=9/28)) and this increased over time to 50% of patients at 2 years and then tails off to 56% at 3 years. However no confidence intervals were reported and the 3 year results are only based on 9 patients so this increase may not be statistically significant. At 6 months, a statistically significant reduction in SEGA volume was seen (median reduction from baseline = 0.8 cm^3 (95% CI = 0.4 to 1.2; p-value<0.001)). A further reduction is shown at 3 years, but it is not clear whether this is statistically significant. No patient had worsening hydrocephalus or worsening symptoms attributable to increased intracranial pressure. No patient needed to undergo surgical resection or other therapy for SEGA. The results on neurocognition and quality of life were inconclusive. As a result of these findings, the FDA approved the use of everolimus for patients with SEGA associated with TSC who are not suitable for surgery. These results do not add any further information to the main results of EXIST-1.

Trelinska et al 2015¹⁶

This is a case series of 15 patients with SEGA associated with TSC who were not amenable to surgery and were treated with everolimus at a hospital in Warsaw in Poland. They found statistically significant reductions in tumour volume at 3 and 6 months. The authors attempt to assess which factors affect response to everolimus treatment, but the study is inadequately powered to do this. These results do not add any further information to the main results of EXIST-1.

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Table 1: Summary of Studies of the use of Everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex

Study	Patients	Intervention	Comparator	Outcomes (CIs and p-values reported where available)
<p>Franz et al 2013^a</p> <p>International multicentre RCT</p>	<p>n=117</p> <p>Inc/ex criteria: Aged 0-65 years with at least one SEGA lesion ≥ 1.0 cm assessed with MRI, and either: - serial radiological evidence of SEGA growth (increase $\geq 25\%$ in SEGA volume), - presence of a new SEGA lesion ≥ 1 cm in longest diameter, - or new or worsening hydrocephalus. Patients had to be medically stable and unlikely to require surgery for SEGA with no critical hydrocephalus or imminent cerebral herniation.</p> <p>Baseline characteristics: Median age = 9.5 years Skin lesions present = 94% Prior SEGA-related surgery = 7%</p> <p>Randomised to everolimus: placebo as 2:1</p>	<p>n=78</p> <p>Everolimus (oral), start dose of 4.5mg/m²/day and subsequently adjusted to attain blood trough concentrations of 5-15 ng/ml</p>	<p>n=39</p> <p>Placebo</p>	<p>Median duration of everolimus exposure = 41.9 weeks (range 24.0–78.9) Median dose intensity of everolimus = 5.9 mg/m² per day (range 2.3–11.8) Median follow-up = 9.7 months</p> <p>SEGA response rate (defined as reduction in the total volume of all target SEGA of 50% or more relative to baseline, in the absence of worsening of non-target SEGA, new lesions of 1cm or greater in diameter, and new or worsening hydrocephalus): 35% (n=27/78) in the everolimus arm compared with 0% (0/39) in the placebo arm Difference = 35% (95% CI 15-52%, p<0.0001) Sub-group analyses showed no statistically significant differences in effect size by antiepileptic drug use, sex or age.</p> <p>Absolute change in frequency of total seizure events per 24-hour EEG from baseline to week 24: 0 in the everolimus arm and 0 in the placebo arm (p=0.2004)</p> <p>SEGA progression (defined as an increase of 25% or more from the nadir volume at baseline; unequivocal worsening of non-target lesions of SEGA; the appearance of new lesions of 1cm or more in diameter; or new or worsening hydrocephalus): Median time to SEGA progression was not reached in either treatment arm. 0% (0/78) progressed in the everolimus arm compared to 15.4% (6/39) in the placebo arm (p=0.0002). Estimated progression-free rates at 6 months were 100% in the everolimus arm and 85.7% in the placebo arm.</p> <p>Skin lesion response rate: 110 had at least one baseline skin lesion. 42% (30/72) in the everolimus arm vs 11% (4/38) in the placebo arm (p=0.0004) had a skin lesion response. All skin lesion responses were incomplete.</p> <p>Angiomyolipoma response: 44 patients had at least one baseline renal angiomyolipoma. 53% (16/30) in the everolimus arm versus none (0/14) in the placebo arm had an angiomyolipoma response.</p> <p>Adverse events: Proportion requiring dose reduction or temporary interruption of treatment: due to adverse events = 49% (38/78) for everolimus vs 10% (4/39) for placebo No adverse events led to discontinuation of the trial. No deaths. Mouth ulceration: 32% (25/78) for everolimus vs. 5% (2/39) for placebo</p>

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<p>Franz et al 2014¹⁰</p> <p>2-year open-label, uncontrolled, extension of EXIST-1 trial</p> <p>Interim data report</p>	<p>n=111</p> <p>Inc/ex criteria: Patients enrolled in EXIST-1 (see inc/ex criteria above) who were treated with at least one dose of everolimus. This included patients randomised to everolimus, those randomised to placebo who crossed-over during the core phase of EXIST-1 or during the open-label extension phase.</p>	<p>n=111</p> <p>Everolimus (oral), start dose of 4.5mg/m²/day and subsequently adjusted to attain blood trough concentrations of 5-15 ng/ml</p>	<p>None</p>	<p>Stomatitis: 31% (24/78) for everolimus vs. 21% (8/39) for placebo Convulsion: 23% (18/78) for everolimus vs. 26% (10/39) for placebo Pyrexia: 22% (17/78) for everolimus vs. 15% (6/39) for placebo Vomiting: 17% (13/78) for everolimus vs. 13% (5/39) for placebo Upper respiratory tract infection: 15% (12/78) for everolimus vs. 18% (7/39) for placebo Diarrhoea: 13% (10/78) for everolimus vs. 5% (2/39) for placebo Rash: 12% (9/78) for everolimus vs. 5% (2/39) for placebo Otitis media: 10% (8/78) for everolimus vs. 5% (2/39) for placebo Pharyngitis: 10% (8/78) for everolimus vs. 3% (1/39) for placebo Amenorrhoea: 38% (3/8) for everolimus vs. 0 (0/5) for placebo</p> <p>Median duration of everolimus exposure = 29.3 months (range 1.9-40.5) Median dose intensity of everolimus = 5.9mg/m² per day (range 1.0-13.7) Median follow-up time = 28.3 months (range 1.9-38.8).</p> <p>SEGA response rate (defined as reduction in the total volume of all target SEGA of 50% or more relative to baseline, in the absence of worsening of non-target SEGA, new lesions of 1cm or greater in diameter, and new or worsening hydrocephalus): Data cut-off = 49% (54/111) 95% CI = 39- 58% Week 12 = 27% (29/106) Week 24 = 37% (39/105) Week 48 = 46% (48/104) Week 96 = 47% (36/76) Week 144 = 38% (11/29)</p> <p>Median time to SEGA response (IQR): 3.58 months (2.83-5.65)</p> <p>Time to SEGA progression: Median time to progression not reached. 8% (9/111) had SEGA progression.</p> <p>Median SEGA volume reduction from baseline (IQR): Week 12 (n=106) = 0.57cm³ (0.23-1.02) Week 24 (n=105) = 0.62cm³ (0.28-1.21) Week 48 (n=104) = 0.64cm³ (0.27-1.31) Week 96 (n=76) = 0.63cm³ (0.27-1.31) Week 144 (n=29) = 0.48cm³ (0.36-1.12)</p> <p>One patient underwent surgery during the study.</p> <p>Adverse events: Number of patients requiring dose reduction or temporary interruption was not reported. 31% (35/111) of patients experienced treatment related grade 3 or 4 adverse events 5% (6/111) of patients were discontinued from the study due to adverse events</p>
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				<p>Stomatitis: 42% (47/111) Mouth ulceration: 29% (32/111) Pneumonia: 13% (14/111) Blood cholesterol rise: 10% (11/111) Amenorrhoea: 18% (5/28)</p> <p>Change in adverse events over time: Any treatment related adverse event (AE); serious adverse event (SAE) Year 1 (n=111) = 97% AE; 21% SAE Year 2 (n=106) = 84% AE; 18% SAE Year 3 (n=75) = 69% AE; 5% SAE Year 4 (n=19) = 26% AE; 0% SAE</p>
Kingswood et al 2014 ¹¹	n= 44	n=30	n=14	
Sub-group analysis of EXIST-1	Inc/ex criteria: Patients enrolled in EXIST-1 (see inc/ex criteria above) who had one or more angiomyolipomata that were ≥1.0 cm in longest diameter	Everolimus (oral), start dose of 4.5mg/m ² /day and subsequently adjusted to attain blood trough concentrations of 5-15ng/ml	Placebo	<p>≥50% angiomyolipoma response rate (defined as reduction in the sum of volumes of all target lesions ≥50% relative to baseline, with no new lesions ≥1 cm in longest diameter, no increase in kidney volume ≥20% and no angiomyolipoma related bleeding of Grade ≥2): Data cut-off = 53.3% (16/30) 95% CI = 34.3-71.7% in the everolimus arm compared to 0% (0/14) 95% CI = 0-23.2% in the placebo arm. Week12 = 56.5% for everolimus vs. 0% for placebo Week 24 = 78.3% for everolimus vs. 0% for placebo Week 48 = 80% for everolimus vs. 0% for placebo</p> <p>≥30% angiomyolipoma response rate: Week12 = 82.6% for everolimus vs. 8.3% for placebo Week 24 = 100% for everolimus vs. 18.2% for placebo Week 48 = 100% for everolimus vs. 16.7% for placebo</p> <p>Median change in AML lesion volume from baseline (range): Week 24: -7.89cm³ (-104.54 to -0.23), compared with 0.65cm³ (-4.10 to 9.01) in the placebo arm. 11.2% (13/116) of patients had mutations in TSC1 (10 in everolimus arm and 3 in placebo arm) 72.4% (84/116) of patients had mutations in TSC2 (55 in the everolimus arm and 29 in the placebo arm). 16.4% (19/116) of patients had no mutation identified (12 in the everolimus arm and 7 in the placebo arm)</p> <p>Location of the mutation had no apparent correlation with SEGA response. No significant difference in response comparing those subjects with truncating vs. non-truncating mutations in either TSC1 or TSC2, those subjects with any TSC2 mutation vs. those with no mutation identified or those subjects with any TSC1 mutation vs. those with any TSC2 mutation (all P>0.2, t-test).</p>
Kwiatowski et al 2015 ¹²	n=116	n=78	n=39	
Sub group analysis of EXIST-1	Inc/ex criteria: Patients enrolled in EXIST-1 (see inc/ex criteria above) with DNA samples available	Everolimus (oral), start dose of 4.5mg/m ² /day and subsequently adjusted to attain blood trough concentrations of 5-15ng/ml	Placebo	<p>SEGA response rate = 75% (6/8)</p>
Kotulska et al	n=8	n=8	n=0	

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2013 ¹³ Case series from EXIST-1	Inc/ex criteria: Patients enrolled in EXIST-1 (see inc/ex criteria above) who were aged 3 years and under who were enrolled into EXIST-1 trial from a centre in Warsaw, Poland	Everolimus (oral), start dose of 4.5mg/m ² /day and subsequently adjusted to attain blood trough concentrations of 5-15ng/ml n=28	Placebo	No SEGA progression was observed in any of the children.
Krueger et al 2010 ¹⁴ Case series (short-term follow-up)	n=28 Inc/ex criteria: 3 years of age or older and had a definitive diagnosis of TSC and serial growth of SEGA (defined as an increase in size, as compared with baseline, on at least two successive MRI scans). Patients also had to be medically stable, without signs of cerebral herniation or critical hydrocephalus. Median age = 11 years (range = 3 to 34) 14% had previously undergone surgery for SEGA	Everolimus (oral), start dose of 3.0 mg/m ² of body surface area, to achieve a trough concentration of 5-15ng/ml	None	<p>Median daily dose of everolimus (range) = 5.6mg/m² (1.5 - 10.5) Median duration of treatment (range) = 21.5 months (4.7 - 34.4)</p> <p>≥50% reduction in SEGA volume At 6 months = 32% (9/28) of patients</p> <p>≥30% reduction in SEGA volume At 6 months = 75% (21/28) of patients</p> <p>SEGA volume median reduction from baseline At 6 months = 0.8 cm³ (95% CI 0.4-1.2; p-value<0.001)</p> <p>No patient had worsening hydrocephalus or worsening symptoms attributable to increased intracranial pressure No patient needed to undergo surgical resection or other therapy for the tumor One patient had initial shrinkage of the tumor (an 18% reduction in volume at 6 months relative to baseline) that was followed by progression (resulting in, at 18 months, a 16% increase relative to baseline).</p> <p>Seizures (clinical and subclinical): Median change from baseline = -1 seizure (p=0.02)</p> <p>Quality of life (as measured by Quality-of-Life in Childhood Epilepsy (QOLCE) questionnaire; score can range from 0 to 100, with higher scores indicating a better quality of life): Mean (±SD) QOLCE scores Baseline = 57.8±14 3 months = 63.4±12.4 6 months = 62.1±14.2</p> <p>Cognition: No changes were seen in intelligence or neuropsychological measurements</p>

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Krueger et al 2013 ¹⁵ Case series (long-term follow-up)	n=28 Inc/ex criteria: 3 years of age or older and had a definitive diagnosis of the tuberous sclerosis complex and serial growth of subependymal giant-cell astrocytoma (defined as an increase in size, as compared with baseline, on at least two successive magnetic resonance imaging [MRI] scans). Patients also had to be medically stable, without signs of cerebral herniation or critical hydrocephalus.	n=28 Everolimus, start dose of 3.0 mg/m ² of body surface area, to achieve a trough concentration of 5-15ng/ml	None	<p>Treatment related adverse events Any = 100% (28/28) Stomatitis = 79% (22/28) Upper respiratory tract infection = 79% (22/28) Sinusitis = 39% (11/28) Otitis media = 36% (10/28) Pyrexia = 29% (8/28) Acneiform dermatitis = 25% (7/28) Diarrhoea = 21% (6/28) Cellulitis = 21% (6/28)</p> <p>Median treatment dose = 5.3 mg/m²/day (range 2.1-12.3) Median treatment duration = 34.2 months (range 4.7-47.1) 3 patients withdrew consent for noncompliance with antiepileptic drug, inability to maintain study visits, and withdrawal of parental consent.</p> <p>≥50% reduction in SEGA volume: At 12 months = 34.6% (9/26) At 24 months = 50% (12/24) At 36 months = 55.6% (5/9)</p> <p>≥30% reduction in SEGA volume: At 12 months = 76.9% (20/26) At 24 months = 79.2% (19/24) At 36 months = 77.8% (7/9)</p> <p>SEGA volume median reduction from baseline (range): At 12 months = 0.85 (0.02-6.05) At 24 months = 0.71 (-0.55-9.600) At 36 months = 1.34 (0.15-4.75)</p> <p>Treatment related adverse events: No adverse events resulted in discontinuation of everolimus therapy. Upper respiratory infections = 85.7% Stomatitis = 85.7% Sinusitis = 46.4% Otitis media = 35.7% Median duration of treatment = 13 months (range 3-24)</p> <p>Median SEGA volume (range) At baseline = 2.70cm³ (0.24-14.30) At 3 months = 0.97 cm³ (0.24-12.20) change from baseline p=0.001 At 6 months = 0.70 cm³ (0.23-4.86) p=0.001 At 12 months = 1.24 cm³ (0.17-4.86)</p>
Trelinska et al 2015 ¹⁶	n=15 Inc/ex criteria: Children with SEGA associated with TSC not amenable to neurosurgery, treated with everolimus in a hospital in Warsaw in Poland.	n=15 Everolimus, start dose calculated according to body surface area which	None	

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	<p>Patients with hepatic impairment were excluded.</p> <p>8 children were previously treated for SEGA (6 with neurosurgery and 2 with everolimus) but everolimus was required due to tumour regrowth.</p>	<p>ranged from 2.5-7.5mg.</p>	<p>No patients required surgery after reduction in tumour volume.</p> <p>Adverse events: Adverse events were seen in 73% (11/15) of patients Stomatitis = 33% (5/15) Upper respirator tract infections = 27% (4/15) Lower respiratory tract infections = 20% (3/15) Hypertension = 20% (3/15) Amenorrhea = 67% of females aged over 13 years (2/3)</p>
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4.2 Trials in progress

A search of clinicaltrials.gov on the 19th of September 2015 showed no, current, ongoing trials for everolimus for SEGA associated with TSC.

4.3 Evidence of cost-effectiveness

No studies were found evaluating the cost-effectiveness of everolimus for the treatment of SEGAs associated with TSC.

Establishing cost-effectiveness is impossible when long-term evidence on clinical outcomes is uncertain.

4.4 Safety

A literature search for studies looking specifically at safety and adverse effects of everolimus on patients with SEGA associated with TSC did not find any relevant studies. Instead adverse event findings from the included RCT have been used and its uncontrolled extension phase to give an idea of long-term safety. Adverse event results are also summarised in Table 1 for each included study.

EXIST-1 Franz et al 2013⁹

The authors reported that the adverse event profile was consistent with the known safety profile of everolimus. The most common adverse events were mouth ulceration and stomatitis, both of which were experienced by around a third of all everolimus patients (mouth ulceration 32% for everolimus vs 5% for placebo; stomatitis 31% vs 21%). Convulsion was also common, but there was little difference observed between the two groups (23% for everolimus vs 26% for placebo). Other common adverse events that were experienced by a higher proportion of patients in the everolimus arm include pyrexia (22% for everolimus vs 15% for placebo), vomiting (17% vs 13%), fatigue (14% vs 3%), diarrhoea (13% vs 5%), rash (12% vs 5%), otitis media (10% vs 5%) and pharyngitis (10% vs 3%). Confidence intervals and p-values were not reported. The most common grade 3 adverse events were stomatitis and pyrexia. Six patients (8%) in the everolimus arm experienced grade 3 (severe) stomatitis compared to one patient in the placebo arm (3%) and 5 patients (6%) experienced grade 3 pyrexia in the everolimus group compared to none in the placebo group. Grade 4 (life threatening) adverse events were very rare. Secondary amenorrhoea lasting from 8 weeks to 14 months was experienced by 38% of girls aged 13 or over in the everolimus group (3 out of 8 girls) compared to 0% (0 out of 5 girls) in the placebo group.

Almost half of all patients in the everolimus arm (49%) compared to 10% in the placebo arm experienced adverse events that required dose reduction or temporary interruption of treatment. This was most commonly due to stomatitis (13 patients), mouth ulceration (6 patients), pyrexia (5 patients) and pneumonia (4 patients). No patients permanently discontinued treatment due to adverse events.

Open label extension of EXIST-1 Franz et al 2014¹⁰

The adverse event profile was similar to that seen in the core phase of EXIST-1, with the most common adverse events being stomatitis (experienced by 42% of patients) and mouth ulceration (29% of patients). These were also the most common reasons for dose reduction or temporary interruption. Grade 3 or 4 adverse events were reported in just over half of patients (51%) and a third (31%) were suspected to be treatment related. The most common treatment-related grade 3 adverse event was stomatitis (8%), followed by pneumonia (7%) and neutropenia (5%). Three

patients (3%) experienced treatment-related grade 4 adverse events, which were pneumonia and neutropenia. Five patients out of 28 females aged 10-55 years (18%) had amenorrhoea which resolved during treatment in all but one case. The authors reported that everolimus had no significant effect on development or sexual maturation. Sixty-four patients (58%) had dose interruptions due to adverse events, and in six patients (5%) treatment was discontinued due to a total of eight adverse events; acinetobacter bacteraemia, aggression, anaemia, increased blood alkaline phosphatase concentrations, neutropenia, pneumonia, sinusitis and viral infection. The frequency of adverse events was shown to decrease with time with 97% of patients experiencing adverse events (21% experienced serious adverse events) in the first year to 26% (0% experienced serious adverse events) in the fourth year. However results for year 4 are only based on 19 patients so they should be treated with caution.

4.5 Summary of section 4

We found one RCT (EXIST-1), which assessed the effectiveness of everolimus in patients with SEGA associated with TSC, and one uncontrolled extension of this trial. The trial was well conducted and of reasonable size. After a minimum treatment time of 6 months, everolimus was found to be more effective than placebo with 35% of patients in the everolimus arm achieving SEGA response compared to none in the placebo arm. No cases of progression of SEGA were seen in the everolimus group compared to 6 cases (15%) in the placebo arm. Adverse events were common, but mostly non-serious and did not result in discontinuation of treatment. Although the extension phase of the trial appears to show the benefits of everolimus are maintained over time, the study is uncontrolled so true long-term effectiveness of everolimus is not known. No studies were found comparing the effectiveness of everolimus to other mTOR inhibitors or surgery.

No studies were found assessing the cost-effectiveness of everolimus.

No ongoing trials were found.

5 Discussion and conclusions

We found one relevant RCT (EXIST-1), which assessed the effectiveness of everolimus in patients with SEGA associated with TSC. The trial was well conducted and of moderate size (117 patients), although some power was lost as patients were randomised in a 2:1 ratio to everolimus versus placebo, presumably to encourage patients to enter the trial. To be included, patients had to have evidence of worsening SEGA, but be unlikely to require surgery with no critical hydrocephalus. The median age of participants was 9.5 years and they were followed-up for a minimum of 6 months (median=9.7 months). The primary outcome was the proportion of patients with SEGA response, which was defined as a reduction in the total volume of all target SEGA of 50% or more relative to baseline, in the absence of worsening of non-target SEGA, new lesions of 1cm or greater in diameter, and new or worsening hydrocephalus. Everolimus was found to be effective with 35% of patients (n=27/78) achieving SEGA response compared to none in the placebo arm (n=0/39) and no cases of progression compared to 15% of patients (n=6/39) in the placebo arm. In addition to its effect on SEGA, everolimus produced significant reductions in skin lesions and kidney tumours. Adverse events were common and although mostly not serious, they caused half of all everolimus patients to temporarily halt treatment or reduce their dose. The most common adverse events were mouth ulceration and stomatitis, both of which were experienced by around a third of all everolimus patients. The findings of the trial appear generalisable to a UK population.

While it is apparent from EXIST-1 that everolimus is effective at shrinking and stabilising SEGAs and this effect seems to be maintained over 3 years with reasonable tolerability, it is very difficult to truly assess its clinical and cost-effectiveness. EXIST-1 only offers randomised evidence for a median follow-up of 10 months as 6 months after the last patient was enrolled all patients in the placebo arm were crossed-over to everolimus. Without a longer-term randomised comparison it is impossible to assess clinical effectiveness, for example how many untreated patients would have had no complications from SEGA or would have eventually been cured by surgery without complications. An ideal trial might randomise patients to everolimus or to a strategy of regular monitoring with surgery if indicated, and then follow these patients up for a long period time measuring clinical outcomes, such as hydrocephalus, seizures, cognition and quality of life. Questions remain about whether treatment with everolimus needs to be life-long, whether tumours will ultimately progress on treatment, and finally the long-term side effects. No reliable data on quality life were found and in the absence of reliable data on long-term clinical outcomes, cost-effectiveness cannot be established.

- 1 Is Everolimus clinically effective in reduction in SEGA tumour volumes and improvement of quality of life in patients with the Tuberous Sclerosis complex compared with no intervention or with other standardised treatments?

There is robust evidence from one well-conducted, moderately sized RCT to show that everolimus is effective at reducing SEGA tumours in the short-term compared to no treatment. The trial found that 35% of patients (n=27/78) in the everolimus arm achieved a reduction in the total volume of SEGA by 50% or more compared with 0% of patients (n=0/39) in the placebo arm (difference = 35% (95% CI = 15 to 52%, p<0.0001). Changes in tumour volumes were not reported so the absolute changes in tumour size are not known. Patients were followed up for a median of ten months and then all placebo patients were crossed-over to everolimus so uncertainty remains around the long-term effectiveness of everolimus. The effect of everolimus on quality of life is not known as we only found one small case series measuring the outcome. No trials were found comparing everolimus to other mTOR inhibitors or surgery.

- 2 Is Everolimus cost effective in patients suffering from SEGA associated with TSC?

No studies were found assessing the cost-effectiveness of everolimus in patients with SEGA associated with TSC. In the absence of data on clinical effectiveness it is impossible to establish cost-effectiveness.

Competing Interest

All SPH authors have completed the ICMJE uniform disclosure form (www.icmje.org/coi_disclosure.pdf) and declare: grants from NHS England to SPH to undertake the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

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6 References

1. National Institute of Neurological Disorders and Stroke. Tuberous Sclerosis Fact Sheet: NIH Publication No. 07-1846 (internet – accessed 3/9/15). http://www.ninds.nih.gov/disorders/tuberous_sclerosis/detail_tuberous_sclerosis.htm
2. Tran L, Zupanc M. Long-Term Everolimus Treatment in Individuals With Tuberous Sclerosis Complex: A Review of the Current Literature. *Pediatric Neurology*. 2015;53(1):23-30.
3. Franz DN. Pharmacologic Management of Tuberous Sclerosis Complex- associated Subependymal Giant Cell Astrocytomas. *Expert Opinion on Orphan Drugs*. 2014;2(1):53-66
4. Jozwiak S, Nabbout R, Curatolo P, on behalf of the participants of the TSC Consensus Meeting for SEGA and Epilepsy Management. Management of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC): Clinical recommendations. *European Journal of Paediatric Neurology*. 2013;17(4):348-52.
5. Krueger D, Northrup H. Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatric Neurology*. 2013;49(4):255-265.
6. O'Callaghan FJ, Shiell AW, Osborne JP, Martyn CN. *Lancet* 1998;351(9114):1490
7. U.S. Food and Drug Administration. Everolimus for Tuberous Sclerosis Complex (TSC). 2012. [internet – accessed on 3/9/15]. <http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm317490.htm>
8. European Medicines Agency. Votubia. [internet – accessed on 3/9/15]. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002311/human_med_001484.jsp&mid=WC0b01ac058001d124
9. Franz D, Belousova E, Sparagana S, Bebin E, 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. *The Lancet*. 2013;381(9861):125-132
10. Franz D, Belousova E, Sparagana S, Bebin E, Frost M, Kuperman R et al. Everolimus for subependymal giant cell astrocytoma in patients with tuberous sclerosis complex: 2-year open-label extension of the randomised EXIST-1 study. *Lancet Oncology*. 2014;15:1513–20
11. Kingswood J, Jozwiak S, Belousova E, Frost M, Kuperman R, Bebin E 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. *Nephrology Dialysis Transplantation*. 2014;29(6):1203-1210.
12. Kwiatkowski DJ, Palmer MR, Jozwiak S, Bissler J, Franz D, Segal S et al. Response to everolimus is seen in TSC-associated SEGAs and angiomyolipomas independent of mutation type and site in TSC1 and TSC2. *European Journal of Human Genetics*. 2015; 1–8.
13. Kotulska K, Chmielewski D, Borkowska J, Jurkiewicz Kuczynski D, Kmiec T et al. Long-term effect of everolimus on epilepsy and growth in children under 3 years of age treated for subependymal giant cell astrocytoma associated with tuberous sclerosis complex. *European Journal of Paediatric Neurology*. 2013;17:479-485.
14. Krueger DA, Care MM, Holland K, Agricola K, Tudor C, Mangeshkar P et al. Everolimus for Subependymal Giant-Cell Astrocytomas in Tuberous Sclerosis. *N Engl J Med* 2010;363:1801-11.

15. Krueger DA, Care MM, Agricola K, Tudor C, Mays M, Franz D. Everolimus long-term safety and efficacy in subependymal giant cell astrocytoma. *Neurology* 2013;80:574-580.
16. Trelinska J, Dachowska I, Kotulska K, Baranska D, Fendler W, Jozwiak S et al. Factors affecting response to everolimus therapy for subependymal giant cell astrocytomas associated with tuberous sclerosis. *Pediatric Blood & Cancer* 2015;62(4):616-621.

7 Search Strategy

Population, Intervention, Comparator and Outcomes (PICO)

P- Patients/ population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Children and adults with SEGA associated with TSC who are not amenable to surgery
I - Intervention Which intervention, treatment or approach should be used?	Everolimus
C - Comparison What is/ are the main alternative/s to compare with the intervention being considered?	No intervention Any other standardised treatments including: Rapamycin
O - Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	Any, including: Reduction in tumour volumes with respect to subependymal giant cell astrocytomas Prevention of growth of SEGA Mortality Morbidity Hydrocephalus Recurrence rate of SEGA Time to onset of benefit/duration of benefit Co benefits:- Reductions in renal angiomyolipoma Improvement in skin rash Quality of life Adverse events Cost-effectiveness

Search date: 5th August 2015

Databases searched: PubMed, Embase, Cochrane Library, Trip and NICE Evidence Search. The searches were limited to the English language and the last 10 years. Letters, editorials, conference papers and case reports were excluded.



Searches

- 1 everolimus/
- 2 (everolimus or afinitor or zortress or votubia).ti,ab.
- 3 1 or 2
- 4 *astrocytoma/ or subependymal giant cell astrocytoma/
- 5 (astroctoma* or sega).ti,ab.
- 6 4 or 5
- 7 3 and 6
- 8 limit 7 to english language