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ORIGINAL RESEARCH ARTICLE

Efficacy, Retention and Tolerability of Everolimus in Patients with Tuberous Sclerosis Complex: A Survey-Based Study on Patients' Perspectives

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Abstract

Background The approval of everolimus (EVE) for the treatment of angiomyolipoma (2013), subependymal giant cell astrocytoma (2013) and drug-refractory epilepsy (2017) in patients with tuberous sclerosis complex (TSC) represents the first disease-modifying treatment option available for this rare and complex genetic disorder.

Objective The objective of this study was to analyse the use, efficacy, tolerability and treatment retention of EVE in patients with TSC in Germany from the patient's perspective.

Methods A structured cross-age survey was conducted at 26 specialised TSC centres in Germany and by the German TSC patient advocacy group between February and July 2019, enrolling children, adolescents and adult patients with TSC.

Results Of 365 participants, 36.7% ($n = 134$) reported the current or past intake of EVE, including 31.5% ($n = 115$) who were taking EVE at study entry. The mean EVE dosage was 6.1 ± 2.9 mg/m^2 (median: 5.6 mg/m^2, range 2.0–15.1 mg/m^2) in children and adolescents and 4 ± 2.1 mg/m^2 (median: 3.7 mg/m^2, range 0.8–10.1 mg/m^2) in adult patients. An early diagnosis of TSC, the presence of angiomyolipoma, drug-refractory epilepsy, neuropsychiatric manifestations, subependymal giant cell astrocytoma, cardiac rhabdomyoma and overall multi-organ involvement were associated with the use of EVE as a disease-modifying treatment. The reported efficacy was 64.0% for angiomyolipoma (75% in adult patients), 66.2% for drug-refractory epilepsy, and 54.4% for subependymal giant cell astrocytoma. The overall retention rate for EVE was 85.8%. The retention rates after 12 months of EVE therapy were higher among adults (93.7%) than among children and adolescents (88.7%; 90.5% vs 77.4% after 24 months; 87.3% vs 77.4% after 36 months). Tolerability was acceptable, with 70.9% of patients overall reporting adverse events, including stomatitis (47.0%), acne-like rash (7.7%), increased susceptibility to common infections and lymphoedema (each 6.0%), which were the most frequently reported symptoms. With a total score of 41.7 compared with 36.8 among patients not taking EVE, patients currently being treated with EVE showed an increased Liverpool Adverse Event Profile. Noticeable deviations in the sub-items 'tiredness', 'skin problems' and 'mouth/gum problems', which are likely related to EVE-typical adverse effects, were more frequently reported among patients taking EVE.

Conclusions From the patients' perspective, EVE is an effective and relatively well-tolerated disease-modifying treatment option for children, adolescents and adults with TSC, associated with a high long-term retention rate that can be individually considered for each patient. Everolimus therapy should ideally be supervised by a centre experienced in the use of mechanistic target of rapamycin inhibitors, and adverse effects should be monitored on a regular basis.

Clinical Trial Registration: This study was registered with the German Clinical Trials Register (DRKS00016045; Universal Trial Number: U1111-1229-4714).

Extended author information available on the last page of the article

Key Points

Everolimus is a well-established disease-modifying therapy for tuberous sclerosis complex that is widely used in Germany for several disease manifestations

Everolimus appears to provide a good effect on drug-refractory epilepsies, subependymal giant cell astrocytoma, angiolipomas and cardiac rhabdomyoma

Over two-thirds of patients reported adverse events with everolimus, with stomatitis as the most frequent symptom (47.0%), followed by immunosuppression and an acne-like rash

Adverse events frequently result in dose reductions, and cause approximately one-quarter of all patients (22.4%) to temporarily discontinue therapy

Retention rates were high over the first 36 months in children, adolescents and adults

1 Introduction

Tuberous sclerosis complex (TSC) is a rare genetic disorder with a prevalence of up to 1 in 5000 individuals that is caused by genetic variations in either the *TSC1* or *TSC2* gene, which result in the loss of function [1–3]. Both genes encode components of the hamartin-tuberin complex and serve as tumour suppressor genes by downregulating cell proliferation and differentiation via mechanistic target of rapamycin (mTOR) [4, 5]. Tuberous sclerosis complex presents as distinct clinical manifestations in various organ systems, typically caused by the impairment of normal organ function by the development of benign rapidly growing tumours [6–8]. Children with TSC often develop severe drug-resistant epilepsy (DRE) shortly after birth or within their first year of life, which is characterised by infantile spasms, focal seizures and comorbid developmental delay, cognitive disabilities and neuropsychiatric symptoms [7–12]. Due to the often severe course of the disease, TSC represents an enormous burden for patients and their caregivers [13]. Moreover, high disease-related direct and indirect costs pose a strain on patients, their caregivers, and the public health systems [14, 15].

Following their discovery in 1975, mTOR inhibitors, such as sirolimus and everolimus (EVE), have increasingly been used to treat various tumour entities and following organ transplantation, supported by research examining the relationship between rapamycin and cell proliferation [16]. Everolimus was approved in 2013 by the European Medicines Agency as a disease-modifying treatment (DMT) for patients with TSC who present with subependymal giant cell astrocytoma (SEGA), which is a low-grade astrocytic brain tumour (astrocytoma) that develops within the ventricle system. The approval of EVE use was extended by the European Medicines Agency to the treatment of renal angiomyolipoma in 2013 and focal seizures associated with DRE in 2017, allowing for the broad use of EVE to treat these three TSC manifestations [17–20]. Outside of these approved indications, EVE is also used off-label to treat other TSC-associated manifestations in severely affected patients, such as severe neuropsychiatric symptoms and cardiac rhabdomyoma (CRM) [21]. In general, the use of EVE in TSC has been shown to be feasible; however, data regarding the efficacy, retention, safety and tolerability of EVE from the patient's perspective are missing, and EVE has been associated with drug-related adverse events (AEs), including severe infections and isolated cases of reported deaths [22]. The aim of the present study was to analyse the use, efficacy, retention and tolerability of EVE among patients with TSC in Germany from the patient's point of view.

2 Methods

2.1 Study Design

This survey enrolled children, adolescents and adults with TSC through the German TSC patient advocacy group (Tuberöse Sklerose Deutschland e.V., Wiesbaden, Germany) and at 26 specialised TSC centres throughout Germany (Berlin, Bochum, Erlangen, Frankfurt, Freiburg, Giessen, Greifswald, Hannover, Herdecke, Heidelberg, Hirschaid, Homburg, Kassel, Kempten, Kiel, Kork, Leipzig, Lingen, Marburg, München, Münster, Neuruppin, Oberhausen, Radeberg [near Dresden], Rostock, Stuttgart, Tübingen, Vogtareuth and Wiesbaden). Written informed consent, obtained either from the patients themselves or from their legal guardians, was mandatory to participate in this study. The diagnosis of TSC was based on the recommendations of the 2012 International TSC Consensus Conference [23]. All patients who did not meet these criteria or for whom relevant data were missing ($n = 11$) were excluded from the study. This study received approval from the Institutional Review Board of Goethe-University and was registered with the German Clinical Trials Register (DRKS00016045; Universal Trial Number: U1111-1229-4714). During conception, conduction and analysis of the present study, the STROBE guidelines (Strengthening The Reporting of Observational Studies in Epidemiology) were closely followed [24] to increase the reliability and accuracy of the data analysis.

2.2 Data Acquisition and Metrics

Questionnaires were provided to adult patients with TSC or their primary caregivers, for example, in the case of a cognitive disability/incapacity, as well as to caregivers of children and adolescents with TSC between February and July 2019. All adult participants and the legal guardians of minor patients with TSC (< 18 years of age) were asked to complete a retrospective paper-based questionnaire referencing the use of EVE and the associated efficacy and tolerability. The questionnaire used in this study was adapted for use in patients with TSC based on established questionnaires that have previously been validated in outcome research among populations of other chronically ill patients [25–28]. To increase the yield of the survey, both multiple-choice and free-text options were allowed to collect any relevant answers. The following options were available for the indication of efficacy for angiomyolipoma, SEGA or others: no effect, size increase, constant size and size decrease. The efficacy for DRE treatment was graded using the following items: no effect and seizure reduction by 25%, 50%, 75% or 100% (complete cessation of seizures). To assess the tolerability of EVE, questions were systematically asked regarding adverse effects. In addition to the options of no AEs, stomatitis and increased susceptibility to common infections (e.g. frequent mild colds, pharyngitis and bronchitis), respondents were provided with the option of indicating and describing other adverse effects. In addition, each participant was asked whether EVE has been reduced or temporarily discontinued because of AEs. For further analysis, participants were divided into different subgroups according to their ages (< 18 years or ≥ 18 years), general exposure to EVE (no exposure or one or more doses of EVE throughout their lifetime, 'lifetime prevalence') and whether they are currently receiving EVE therapy, using the study entry date as the reporting date. All information used in the study was based on the written statements provided by the patients themselves or their caregivers. Drug-related AEs were assessed using a free specification option and by employing the Liverpool Adverse Event Profile (LAEP). The LAEP is a well-established, 19-item self-report questionnaire that was initially developed to monitor the frequency and severity of common adverse effects associated with anti-seizure drugs (ASDs) and can also be used in other disorders associated with epilepsy [29, 30]. To allow for the basal distinction between AE categories associated with EVE and not caused by the concomitant intake of ASDs, the LAEP and its significant sub-items were also calculated separately for a subgroup of patients who were not taking ASDs. Health-related quality of life (HRQOL) was accessed using the well-established, age-specific by-proxy KINDL questionnaire for children and adolescents in the age group of ≥ 4–17 years and the visual analogue scale of EQ-5L-5D (EuroQOL Group) for adult patients (≥ 18 years of age). In both questionnaires, HRQOL values can range between 0 (very poor) and 100 (very good) [31–33]. Treatment retention at study entry was calculated as the ratio of the number of patients reporting ongoing EVE therapy at the time of study enrolment to the number of patients who reported any lifetime prevalence of EVE.

As no reliable data were available for possible interactions between EVE and other drugs, this relationship or the attribution of fatigue in this regard could not be investigated within the scope of the study. This study assessed TSC relevant laboratory parameters, for example, cholesterol, however, these were very sparsely reported by patients or their caregivers precluding a statistical analysis.

2.3 Data Entry and Statistical Analysis

Statistical analysis was performed in SPSS Statistics 27 (IBM Corp., Armonk, NY, USA) using the non-parametric Kruskal–Wallis rank test to determine significant differences between ordinary items. For the comparison of processed data, an unpaired T-test was performed using the mean, standard deviation and number (n). After post hoc corrections for multiple testing using the Benjamini–Hochberg method [34, 35], p values < 0.05 were regarded as significant. As the study design does not allow for a comparison of factors before and after/on EVE therapy, a multivariate analysis stepwise backwards regression based on all sociodemographic and disease-specific aspects as well as ASD number and AEs under EVE was used to identify factors that influence LAEP and HRQOL at the best possible rate [36]. Graphs were created using GraphPad Prism 7 (GraphPad Software, San Diego, CA, USA) and arranged using PixelmatorPro (Pixelmator Team, Vilnius, Lithuania).

3 Results

3.1 Sociodemographic Data and Disease-Specific Aspects

Overall, 365 participants were enrolled in this analysis. The mean age of the total study population was 22.1 ± 15.4 years (median: 19.0 years, range: 0.7–78.0 years), with an equal sex distribution (49.3% female, 50.7% male). The mean age at the time of TSC diagnosis was 6.2 ± 12.0 years (median: 1.0 years), from a prenatal diagnosis at − 0.33 years to 66 years. The mean age at the time of initial TSC manifestation was 3.3 ± 9.0 years (median: 1 year), from a prenatal manifestation at − 0.25 years to 66 years. Most patients (38.4%, $n = 140$) reported a genetic variation in *TSC2,* including eight patients (2.2%) reporting the *TSC2/PKD1* contiguous gene (*PKDTS*), whereas 15.1% ($n = 55$) reported a genetic

variation in *TSC1*. The subgroup of children and adolescents with TSC comprised 166 patients (45.5%), with a mean age of 9.3 ± 5.0 years (median: 9.6 years, range 0.7–17.9 years), 47.0% of whom were female ($n = 78$). The subgroup of adults with TSC contained 199 patients (54.5%), with a mean age of 32.8 ± 12.7 years (median: 30 years, range 18–78 years).

3.2 Use of mTOR Inhibitors

Overall, 134 patients (36.7%) reported the intake of at least one dose of EVE during their lifetimes (lifetime prevalence), and 115 (31.5%) patients reported using EVE at the time of study entry. The mean current dose of EVE was 6.1 ± 3.4 mg per day (median: 5.0 mg per day, range 0.5–15 mg per day), with a mean dose in the subgroup of children and adolescents of 5.1 ± 2.9 mg per day (median: 5 mg per day, range 0.5–12.5 mg per day) and a mean dose in the adult subgroup of 6.8 ± 3.5 mg per day (median: 5 mg per day, range; 1.5–15.0 mg per day). These values corresponded with a mean dosage of 4.9 ± 2.5 mg/m^2 (median: 4.2 mg/m^2, range 0.8–15.1 mg/m^2) for all patients, a mean of 6.1 ± 2.9 mg/m^2 (median: 5.6 mg/m^2, range 2.0–15.1 mg/m^2) among children and adolescents, and a mean of 4 ± 2.1 mg/m^2 (median: 3.7 mg/m^2, range 0.8–10.1 mg/m^2) among adult patients. Detailed sociodemographic and disease-specific characteristics of all cohorts are provided in Table 1.

Of note, systemic sirolimus was reported to be used in five female patients (1.4%, mean age of 22.0 ± 16.3 years), none of whom was treated with EVE. Sirolimus in these patients was most often associated with the presence of lymphangioleiomyomatosis, consistent with reported benefits of sirolimus in case reports and a randomised controlled trial [37–39].

3.3 Univariate Analysis of Sociodemographic and TSC-Specific Characteristics Associated with EVE Therapy

Univariate analysis revealed that EVE was frequently used in patients with a disease manifestation within the first year of life ($p = 0.028$), in patients diagnosed with angiomyolipoma ($p = 0.006$), DRE ($p = 0.006$), SEGA ($p = 0.006$), CRM ($p = 0.012$) or neuropsychiatric symptoms ($p = 0.012$), and in patients with four or more affected organ systems ($p = 0.006$). Everolimus therapy was also significantly frequently reported in patients using anticonvulsive polytherapy. Lymphangioleiomyomatosis was reported by 22 female patients, but its prevalence was not significantly associated with EVE therapy ($p = 0.699$). No other tested parameters were significantly associated with EVE use (Table 1). Health-related quality of life was lower in adult patients with an EVE lifetime prevalence, with a mean value of 58.9 ± 21.0 (median: 60.0) compared with patients not exposed to EVE (mean 68.3 ± 19.5, median: 70.0, $p = 0.010$). The best fit ($F = 6.112$, $p = 0.004$) of multivariate stepwise regression analysis resulted in a model with two remaining factors, i.e. presence of EVE-associated AEs ($p = 0.089$, odds ratio [OR] 1.728) and active EVE treatment on study enrolment ($p = 0.002$, OR 3.227). Health-related quality of life among children and adolescents did not differ between patients with and without EVE exposure ($p = 0.460$) and the multivariate analysis did not identify a model reaching a level of statistical significance. The best fit ($F = 2.516$, $p = 0.082$) was achieved in a model with AEs under EVE therapy as most relevant, but also a not-significantly contributing factor ($p = 0.057$, OR 1.996). No overall differences in the numbers of ambulatory visits or blood draws were identified between patients with and without EVE exposure ($p = 0.862$ and $p = 0.061$, respectively).

3.4 Indications for EVE Therapy

The majority of patients reported the intake of EVE because of multiple TSC-related symptoms (56%, $n = 75$), whereas only 43.3% ($n = 58$) reported a single indication for mTOR inhibitor therapy. According to patients or their caregivers, the most common indications for systemic EVE therapy were DRE (53.0%, $n = 71$), angiomyolipoma (52.2%, $n = 70$) and SEGA (38.8%, $n = 52$), followed by CRM (12.7%, $n = 17$), dermal TSC manifestations (9.0%, $n = 12$) and cerebral tubers (3.7%, $n = 5$). Angiomyolipoma was significantly more frequently reported as an EVE indication among adults than among children and adolescents ($p = 0.007$), whereas no other indication showed an age group dependence. Lymphangioleiomyomatosis was not reported as an explicit treatment indication by any participants. A detailed overview of the reported indications for EVE therapy is provided in Table 2.

3.5 Efficacy of EVE Therapy

For the three most common indications, DRE, SEGA and angiomyolipoma, an effect attributed to EVE was reported by 66.2%, 54.4% and 64.0% of participants, respectively, including reductions in seizure frequency, reductions in growth sizes or the prevention of further growths. The reported efficacies of EVE for CRM (14.2%) and angiofibroma (5.1%) were lower. No significant difference was identified between the two age subgroups regarding EVE efficacy for frequent indications. A detailed overview of EVE efficacy is provided in Table 3.

Table 1 Sociodemographic and TSC-specific aspects, according to treatment with everolimus

	All patients ($n = 365$)	No EVE ($n = 231$)	EVE ($n = 134$)	p value[a]
Sociodemographic aspects, % (*n*)				
Age category, years				
< 18	45.5 (166)	46.3 (107)	44.0 (59)	0.699
≥ 18	54.5 (199)	53.7 (124)	56.0 (75)	
Sex				
Female	49.3 (180)	50.6 (117)	47.0 (63)	0.649
Male	50.7 (185)	49.4 (114)	53.0 (71)	
Disease manifestation, years				
<1	43.6 (159)	38.1 (88)	53.0 (71)	0.028
≥ 1	48.2 (176)	52.8 (122)	40.3 (54)	
Disease duration, years				
< 15	45.2 (165)	46.8 (108)	42.5 (57)	0.530
≥ 15	46.6 (170)	44.2 (102)	50.7 (68)	
Disease-specific aspects, % (*n*)				
TSC mutation				
TSC1[b]	15.1 (55)	14.7 (34)	15.7 (21)	0.699
TSC2[b]	38.4 (140)	37.7 (87)	39.6 (53)	
n.a.	46.6 (170)	47.6 (110)	44.8 (60)	
Organ manifestation				
Kidney	63.8 (233)	59.3 (137)	71.6 (96)	0.056
Angiomyolipoma	52.3 (191)	45.5 (105)	64.2 (86)	0.006
CRF	7.1 (26)	8.2 (19)	5.2 (7)	0.528
Renal cysts	36.7 (134)	35.1 (81)	39.6 (53)	0.599
Haematuria	3.0 (11)	3.5 (8)	2.2 (3)	0.649
Anaemia	3.8 (14)	3.5 (8)	4.5 (6)	0.699
Epilepsy	82.2 (300)	81.0 (187)	84.3 (113)	0.599
Refractory	43.6 (159)	35.5 (82)	57.5 (77)	0.006
Psychiatric	50.4 (184)	44.2 (102)	61.2 (82)	0.012
Structural brain	74.8 (273)	71.0 (164)	81.3 (109)	0.063
SEGA	37.0 (135)	29.0 (67)	50.7 (68)	0.006
Tuber	38.0 (139)	38.5 (89)	37.3 (50)	0.818
Skin	90.4 (330)	91.3 (211)	88.8 (119)	0.599
Heart	58.4 (213)	50.6 (117)	71.6 (96)	0.006
CRM	42.2 (154)	36.4 (84)	52.2 (70)	0.012
Cardiac arrhythmia	7.9 (29)	8.2 (19)	7.5 (10)	0.232
Hypertension	16.7 (61)	13.4 (31)	22.4 (30)	0.065
Lung	6.0 (22)	5.6 (13)	6.7 (9)	0.699
LAM	6.0 (22)	5.6 (13)	6.7 (9)	0.699
Others	34.5 (126)	30.3 (70)	41.7 (56)	0.065
Eye disease	27.9 (102)	25.1 (58)	32.8 (44)	0.175
Obesity	19.2 (70)	20.3 (47)	17.2 (23)	0.599
Number of affected organ systems				
1–3	24.7 (90)	32.0 (74)	11.9 (16)	0.006
≥ 4	75.3 (275)	68.0 (157)	88.1 (118)	

CRF chronic renal failure, *CRM* cardiac rhabdomyoma, *EVE* everolimus, *LAM* lymphangioleiomyomatosis, *n.a.* not available, *SEGA* subependymal giant cell astrocytoma, *TSC* tuberous sclerosis complex

[a]Calculated between EVE and non-EVE subgroups using the Kruskal–Wallis test with post hoc correction for multiple testing using the Benjamini–Hochberg method

[b]Calculated between *TSC1* and *TSC2*

3.6 Safety and Tolerability of EVE Therapy

Overall, 70.9% ($n = 95$) of all patients reported AEs during EVE therapy, which led to a dose reduction or temporary discontinuation in 22.4% ($n = 30$). Adverse events were significantly more frequently reported among adult patients than among children and adolescents ($p = 0.036$). The most frequently reported AEs were stomatitis (47.0%, $n = 63$), acne-like rash (7.7%, $n = 10$), general symptoms of immunosuppression (6.0%, $n = 8$), lymphoedema (6.0%, $n = 8$) and the deterioration of a patient's general condition (5.2%, $n = 7$). Wound-healing difficulties were reported by three patients (2.2%). The relative frequencies of each AE did not differ significantly between the minor patients and adult patients with TSC in our cohort. Detailed information regarding AE frequency as well as general safety and tolerability of EVE therapy is provided in Tables 4 and 5.

The mean number of ASDs being used was 1.8 ± 0.78 among the total population, including 1.7 ± 0.8 among patients not currently taking EVE and 2.0 ± 0.74 among patients currently taking EVE ($p = 0.043$). In the subgroup of patients currently taking EVE, 24.3% reported no concomitant ASD intake, whereas 18.2% stated the use of one ASD, and 57.4% reported the use of two or more ASDs. Among patients not currently being treated with EVE, 27.6%, 33.2% and 39.2%, respectively reported the use of zero, one or multiple ASDs. Further information regarding the ASD regimes and the corresponding LAEP scores is provided in Table 5.

The mean LAEP score was 38.2 ± 10.9 (median: 37.0) for all enrolled patients. The mean LAEP score was significantly higher among patients currently being treated with EVE (mean: 41.7 ± 11.9) compared with patients not receiving EVE treatment (mean; 36.8 ± 10.2, $p = 0.011$). Significant differences in the LAEP score were observed between patients without concomitant ASD therapy being currently treated or not treated with EVE (EVE 41.4 vs no EVE 34.2, $n = 97$; $p = 0.003$). Comparing patients taking an ASD monotherapy, the LAEP score was significantly higher in those taking EVE (EVE = 40.7 vs no EVE = 37.0, $n = 104$, $p = 0.003$). The LAEP score was also significantly higher in patients taking EVE and an ASD polytherapy (EVE = 42.3 vs no EVE = 38.5, $n = 164$, $p = 0.003$). When examining individual LAEP items, the EVE population revealed significantly higher scores for 'tiredness' ($p = 0.006$), 'problems with the skin' ($p = 0.019$), 'trouble with mouth/gums' ($p = 0.006$) and 'sleepiness' ($p = 0.006$) compared with patients not using EVE. In patients without concomitant ASD therapy, only 'tiredness' ($p = 0.010$), 'problems with the skin' ($p = 0.024$) and 'trouble with mouth/gums' ($p = 0.005$) remained significant. Detailed information describing the LAEP results, and associated items are provided in Table 5 and displayed in Fig. 2. The best fit ($F = 11.431$, $p < 0.001$) of multivariate regression analysis resulted in a model with three remaining factors, i.e. number of concomitant ASDs ($p = 0.062$, OR 1.931), presence of AEs ($p = 0.005$, OR 2.987) and presence of psychiatric comorbidities ($p = 0.001$, OR 3.819).

3.7 Duration and Retention of EVE Therapy

Therapeutic retention at study entry was 85.8%, as 115 were still using EVE therapy of 134 patients with a lifetime prevalence of EVE. Among all patients with a known

Table 2 Frequent indications for everolimus therapy in all patients exposed to everolimus

	Total ($n = 134$)	Children ($n = 59$)	Adults ($n = 75$)	p value[b]
Number of indications, % (n)[a,c]				
1	43.3 (58)	40.7 (24)	45.3 (34)	0.983
2	30.6 (41)	35.6 (21)	26.7 (20)	
≥ 3	25.4 (34)	22.0 (13)	28.0 (21)	
Indication, % (n)[a]				
DRE	53.0 (71)	66.1 (39)	42.7 (32)	0.263
Angiomyolipoma	52.2 (70)	22.0 (13)	76.0 (57)	0.007
SEGA	38.8 (52)	44.1 (26)	34.7 (26)	0.560
CRM	12.7 (17)	10.2 (6)	14.7 (11)	0.543
Dermal manifestation	9.0 (12)	15.3 (9)	4.0 (3)	0.282
Cerebral tuber	3.7 (5)	1.7 (1)	5.3 (4)	0.437

CRM cardiac rhabdomyoma, *DRE* drug-refractory epilepsy, EVE everolimus, *SEGA* subependymal giant cell astrocytoma

[a]Calculated for patients who reported one or more indication for EVE therapy ($n = 60$)

[b]Calculated between EVE and non-EVE subgroups using the Kruskal–Wallis test with post hoc correction for multiple testing using the Benjamini–Hochberg method

[c]Calculated over all given sub-items

Table 3 Reported efficacy of everolimus therapy on different organ manifestations in all patients exposed to everolimus

	Total ($n = 134$)	Children ($n = 59$)	Adults ($n = 75$)	p value[b]
Drug-refractory epilepsy, % (n)[a]	($n = 77$)	($n = 38$)	($n = 39$)	
Attributable effect on seizure reduction	66.2 (51)	71.1 (27)	61.5 (24)	0.289
Seizure reduction < 50%	22.0 (17)	18.4 (7)	25.6 (10)	
Seizure reduction ≥ 50%	33.8 (26)	39.5 (15)	28.2 (11)	
Seizure free	10.4 (8)	13.2 (5)	7.7 (3)	
Subependymal giant cell astrocytoma, % (n)[a]	($n = 68$)	($n = 30$)	($n = 38$)	
Attributable effect	54.4 (37)	73.3 (22)	39.5 (15)	0.989
Size reduction	29.4 (20)	40.0 (12)	21.1 (8)	
Constant size	25.0 (17)	33.3 (10)	18.4 (7)	
Angiomyolipoma, % (n)[a]	($n = 86$)	($n = 26$)	($n = 60$)	
Attributable effect	64.0 (55)	38.5 (10)	75.0 (45)	0.070
Size reduction	29.1 (25)	3.8 (1)	40.0 (24)	
Constant size	34.9 (30)	34.6 (9)	35.0 (21)	
Cardiac rhabdomyoma, % (n)[a]	($n = 70$)	($n = 43$)	($n = 27$)	
Attributable effect	14.2 (10)	14.0 (6)	14.8 (4)	0.987
Size reduction	12.8 (9)	11.6 (5)	14.8 (4)	
Termination of cardiac arrhythmia	1.4 (1)	2.3 (1)	0.0 (0)	
Angiofibroma, % (n)[a]	($n = 99$)	($n = 30$)	($n = 69$)	
Size reduction	5.1 (5)	0.0 (0)	7.2 (5)	

[a]Calculated based on the number of patients reporting the individual tuberous sclerosis complex manifestation and the intake of everolimus

[b]Calculated using the Kruskal–Wallis test with post hoc correction for multiple testing using the Benjamini–Hochberg method for the overall attributable effect

Table 4 Safety and tolerability of everolimus treatment in all patients exposed to everolimus

	Total ($n = 134$)	Children ($n = 59$)	Adults ($n = 75$)	p value
Severity of AEs, % (n)[a]				
Patients with AEs	70.9 (95)	59.3 (35)	80.0 (60)	0.036
AEs leading to EVE reduction	22.4 (30)	20.3 (12)	24.0 (18)	0.368
AEs leading to temporally EVE discontinuation	22.4 (30)	27.1 (16)	18.7 (14)	0.960
Frequent AEs, % (n)[a]				
Stomatitis	47.0 (63)	40.7 (24)	52.0 (39)	0.448
Acne-like rash	7.7 (10)	1.7 (1)	12.0 (9)	0.090
Symptoms of immunosuppression	6.0 (8)	13.6 (8)	9.3 (7)	0.561
Lymphoedema	6.0 (8)	3.4 (2)	8.0 (6)	0.449
Deterioration of general condition	5.2 (7)	1.7 (1)	8.0 (6)	0.368
Diarrhoea	4.5 (6)	3.4 (2)	5.3 (4)	0.757
Fever	3.7 (5)	6.8 (4)	1.3 (1)	0.368
Oral aphthae	3.7 (5)	1.7 (1)	5.3 (4)	0.448
Pneumonia	3.0 (4)	1.7 (1)	4.0 (3)	0.602
Wound-healing difficulties	2.2 (3)	1.7 (1)	2.7 (2)	0.809
Extensive coughing	1.5 (2)	3.4 (2)	0.0 (0)	0.372
Hair loss	1.5 (2)	1.7 (1)	1.3 (1)	0.896
Inflammation in the genital area	0.7 (1)	1.7 (1)	0.0 (0)	0.448
Molluscum contagiosum	0.7 (1)	1.7 (1)	0.0 (0)	0.448

AEs adverse events, *EVE* everolimus

[a]Calculated per 134 patients that have reported the intake of at least 1 dose of EVE

[b]Calculated using the Kruskal–Wallis test with post hoc correction for multiple testing using the Benjamini–Hochberg method

EVE start date and either currently using EVE therapy or with a reported date of withdrawal, the retention rates were 91.4% (n = 106/116) after 12 months, 84.5% (n = 98/116) after 24 months and 82.8% (n = 96/116) after 36 months, with a reported mean EVE therapy duration of 1210 ± 991 days (median: 821 days, range 1–3883 days). Everolimus therapy retention was significantly higher for adult patients (p = 0.049) compared with children and adolescents. More information regarding EVE therapy duration and retention is provided in Table 6. A Kaplan–Meier diagram illustrating EVE therapy retention for the total study population and for both age-related subgroups is displayed in Fig. 1.

Table 5 Univariate analysis of a relationship between the LAEP score and the current intake of everolimus in patients with and without concomitant use of anti-seizure drugs

	All patients (n = 365)		No EVE (n = 250)		EVE (n = 115)		p value[a]
	Mean	± SD	Mean	± SD	Mean	± SD	
LAEP items							
Total score	38.2	10.9	36.8	10.2	41.7	11.9	0.009
Total score[b]	36.6	11.6	34.2	11.1	41.4	11.2	0.013
Unsteadiness	1.9	1.0	1.8	1.0	2.0	1.1	0.058
Tiredness	2.6	1.9	2.4	1.0	2.9	1.0	0.006
Tiredness[b]	2.6	1.0	2.3	1.0	3.0	1.0	0.010
Restlessness	2.4	1.1	2.3	1.1	2.6	1.1	0.064
Feelings of aggression	2.3	1.0	2.2	1.0	2.5	1.1	0.067
Nervousness	2.4	1.0	2.3	1.0	2.5	1.0	0.096
Headache	1.9	0.9	1.9	0.9	2.0	0.9	0.575
Hair loss	1.3	0.8	1.3	0.7	1.4	0.9	0.264
Problems with the skin	2.3	1.1	2.2	1.1	2.5	1.0	0.019
Problems with the skin[b]	2.2	1.2	2.0	1.2	2.7	1.2	0.024
Double/blurred vision	1.5	0.8	1.4	0.7	1.7	1.0	0.064
Upset stomach	1.8	0.9	1.7	0.9	1.9	1.0	0.239
Trouble with mouth/gums	2.1	1.1	1.9	1.0	2.5	1.1	0.006
Trouble with mouth/gums[b]	1.9	1.0	1.7	0.9	2.5	1.0	0.005
Difficulty concentrating	2.8	1.1	2.7	1.1	2.9	1.0	0.327
Tremor, shaky hands	1.7	1.0	1.6	0.9	1.8	1.1	0.253
Weight gain	1.8	1.1	1.8	1.1	1.9	1.1	0.242
Dizziness	1.6	0.8	1.5	0.8	1.7	0.9	0.253
Sleepiness	2.0	1.0	1.8	1.0	2.3	1.1	0.006
Sleepiness[b]	1.9	1.0	1.8	1.0	2.2	1.0	0.062
Symptoms of depression	1.6	0.9	1.5	0.9	1.7	1.0	0.117
Memory problems	2.2	1.1	2.1	1.1	2.3	1.1	0.288
Disturbed sleep	2.3	1.1	2.2	1.1	2.4	1.1	0.120
Oedema, other	1.2	1.2	1.1	1.1	1.4	1.4	0.120
Use of ASDs							
Mean number of ASDs ± SD	1.8	0.78	1.71	0.79	2.03	0.74	0.043
Number of ASD % (n)							
0 (no intake)	26.6 (97)		27.6 (69)		24.3 (28)		0.006
1 (ASD monotherapy)	28.5 (104)		33.2 (83)		18.2 (21)		
≥ 2 (ASD polytherapy)	44.9 (164)		39.2 (98)		57.4 (66)		
LAEP per ASD regime							
0 (no intake)	36.6	11.6	34.2	11.1	41.4	11.2	0.003
1 (ASD monotherapy)	37.7	10.5	37.0	9.9	40.7	13.0	0.003
≥ 2 (ASD polytherapy)	39.9	10.7	38.5	9.5	42.3	12.1	0.003

ASD anti-seizure drug, *EVE* everolimus, *LAEP* Liverpool Adverse Event Profile, *SD* standard deviation

[a]Calculated using the Kruskal–Wallis test with post hoc correction for multiple testing using the Benjamini–Hochberg method

[b]Calculated for patients without the intake of concomitant ASDs (total all patients n = 97; no EVE n = 69; EVE n = 28)

4 Discussion

In line with the licensing guidelines established by the European Medicines Agency, EVE was predominantly used to treat DRE, SEGA and angiomyolipoma [22, 40]. The age-related increase in the use of EVE to treat angiomyolipoma is consistent with the increasing extent and severity of secondary chronic kidney disease during the course of TSC [41, 42]. In addition, the occasional off-label use of EVE to treat other relevant TSC manifestations, such as CRM or severe neuropsychiatric symptoms, was also reported, which supports the use of EVE as a feasible, safe and well-tolerated therapeutic option after an individual benefit-risk assessment [43, 44]. Therapy with EVE was typically associated with more than one disease manifestation in most patients and was associated with a lower HRQOL among adult patients, which is in line with previous studies and indicates that EVE is used more frequently among patients with a higher number of affected organs or more severe disease manifestations [45]. Because cutaneous TSC manifestations are predominantly treated topically with sirolimus, the low number of patients stating a dermal manifestation as an indication for EVE therapy in our study was reasonable [46]; however, beneficial effects of oral mTOR inhibitors against angiofibroma and shagreen patches have recently been demonstrated in patients with skin tumours as the primary disease manifestation and as a secondary effect in individuals being treated with EVE due to SEGA and angiomyolipoma [47, 48].

The efficacy of EVE for the treatment of various TSC symptoms has been extensively studied during the last years [49]. In the present study, efficacy was remarkably high for the treatment of DRE, SEGA and angiomyolipoma, with over 50% of patients being treated for each symptom reporting an effect that could be attributed to EVE therapy. Using the criteria of a ≥ 50% seizure reduction as an established measure for therapeutic efficacy in epilepsy, the 33.8% efficacy reported in this study is in line with previous studies showing seizure reductions ≥ 50% in between 30 and 50% of the study populations of most of the larger studies [50–58]. Although a lively debate is ongoing regarding how long EVE treatment should be continued before an effect on seizures can be expected, our data show that treatment success can be achieved within an interval of 1–3 years [59]. The responder rate is comparable to other modern ASDs, such as brivaracetam, perampanel, eslicarbazepine acetate or cenobamate, which highlights the potential of EVE treatment for TSC-related DRE [60–70]. In SEGA, size reductions under EVE therapy have frequently been used as therapeutic success markers. In the present cohort, a size reduction was reported for 29% of the participants, which is in line with previous publications reporting a treatment response for 32–42% of cases [71–73]. Size reductions or the prevention of further growth in TSC-related angiomyolipoma was reported by 64% of the current study

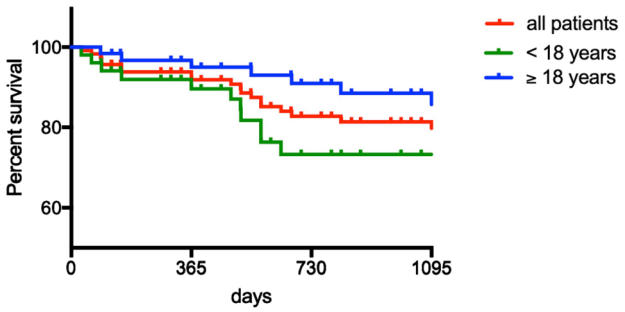

Fig. 1 Everolimus therapy retention displayed as a Kaplan–Meier survival diagram for minor patients (n = 53) and adult patients (n = 63) with tuberous sclerosis complex. Retention at study entry was 85.8%, retention rates after 1, 2 and 3 years of everolimus therapy were 91.4%, 84.5% and 82.8%, respectively. Retention in adult patients was significantly better than retention in children and adolescents (n = 116, log-rank-test, p = 0.049)

Table 6 Everolimus therapy adherence and retention

	All patients (n = 116)	Children (n = 53)	Adults (n = 63)	p value
Intake duration, days[a]				
Mean ± SD	1210 ± 991	949 ± 874	1424 ± 1035	0.049[b]
Median	821	577	1111	
Range	1–3883	1–3103	89–3883	
Retention rates, % (n)[a]				
First year (at 365 days)	91.4 (106)	88.7 (47)	93.7 (59)	
Second year (at 730 days)	84.5 (98)	77.4 (41)	90.5 (57)	
Third year (at 1095 days)	82.8 (96)	77.4 (41)	87.3 (55)	

EVE everolimus, *SD* standard deviation

[a]Calculated based on all patients with a defined starting and endpoint for EVE therapy or ongoing therapy

[b]Calculated using the log-rank test based on all patients with a defined starting and endpoint for EVE therapy or ongoing therapy

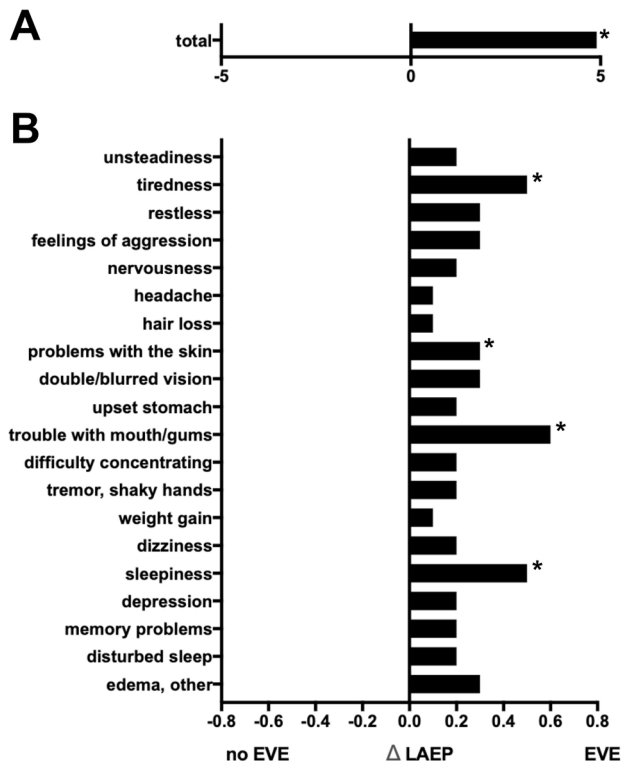

Fig. 2 Deviation of the mean Liverpool Adverse Event Profile (LAEP) total score (**A**) and sub-scores (Δ LAEP, **B**) between patients with tuberous sclerosis complex currently treated with and without everolimus (EVE). A deviation of the bar to the right indicates a higher scale value in the EVE group, indicating a higher burden due to drug-related adverse events. All significant deviations are marked with an *asterisk* (*; $p < 0.05$). The analysis of only those patients without the concomitant intake of anti-seizure drugs revealed that the differences in the LAEP total score and those in the sub-scores of 'tiredness', 'problems with the skin' and 'trouble with mouth/gum' remained significant, indicating relevant EVE-related adverse-event burden for these subscales

participants, which is comparable to the published responder rates of 50–60%. In angiomyolipoma, a possible benefit of low-dose EVE therapy (5 mg) has recently been reported for adult patients, which resulted in a similar efficacy compared with high-dose therapy (10 mg) and was associated with a more favourable AE profile [74]. A valid comparison of the efficacy of EVE treatment for rarer TSC-related indications, such as CRM, tubers and neuropsychiatric symptoms, cannot be adequately performed because of the low numbers reported in this study; however, for the treatment of CRM, case reports describing newborns and infants have shown an individual benefit of EVE treatment against CRM, with a frequently reported recurrence after EVE discontinuation [75, 76]. Lymphangioleiomyomatosis was rarely reported in the present cohort and was never reported as an indication for EVE therapy; therefore, the effect of EVE for lymphangioleiomyomatosis treatment could not be assessed; however, several case reports and a randomised controlled trial have demonstrated the effects of mTOR inhibitor treatment on lymphangioleiomyomatosis in general [77].

Health-related quality of life was lower in adult patients with an EVE lifetime prevalence, compared with patients not exposed to EVE. A multivariate analysis revealed a current EVE treatment at study enrolment as an individual contributing factor for lower HRQOL. This effect could not be determined in children and adolescents with TSC, which may be owing to the general complexity of measuring HRQOL in children and adolescents [78]. To our knowledge, this is the first study highlighting this aspect, in contrast to other studies that have revealed no effect of EVE treatment on HRQOL in patients with neuroendocrine tumours [79].

Safety and tolerability are important issues for EVE therapy, as drug-related AEs have frequently been reported, although the frequency of AEs in controlled trials appears to be higher than those reported in post-marketing studies [58, 80]. Comparable to previously reported retrospective studies, over 70% of patients in our study reported EVE-related AEs, which were more frequently reported (80%) among the adult cohort than among children and adolescents (59%) [18, 57, 81]. In addition to a potential increased willingness to report AEs among adult patients, the underestimation of AEs among children and adolescents due to by-proxy recording of AEs based on the responses of parents and guardians may be a factor in this difference, although this appears to be unlikely according to the literature [82, 83]. In line with the most pivotal and post-marketing studies, frequently reported AEs included stomatitis, symptoms of immunosuppression, trivial infections and an acne-like rash [17, 18, 51]. In the present cohort, frequent dose reductions in response to AEs were reported, which is in line with current international recommendations for the management of relevant AEs during mTOR inhibitor therapy [80]. As another approach to assess tolerability, the individual LAEP was calculated to characterise the AE profiles of patients being treated with or naïve to EVE. Patients who reported EVE exposure showed a significantly higher LAEP total score, indicating a higher burden due to AEs (Table 5, Fig. 2A). Moreover, several LAEP sub-items (Table 5, Fig. 2B) were significantly increased in the EVE-exposed population. Because of the study design, no reliable causal relationships can be established between these individual LAEP items and the use of EVE; however, the increased sub-scores observed for 'skin problems' and 'problems of the mouth or gums' appear to match the characteristic AEs that have been reported for mTOR inhibitors [80]. Other nonspecific symptoms, such as 'dizziness', 'fatigue', 'drowsiness' and 'restlessness', might reflect a more severely affected patient collective or be associated with AEs caused by other medications [84]. To approach the problem of the

lack of a causal relationship between LAEP and EVE exposure, a multivariate backward stepwise regression was performed highlighting the presence of EVE-associated AEs and of psychiatric comorbidities as relevant contributors. These results further support the impact of EVE therapy on LAEP in patients with TSC. The correlation of high LAEP scores and psychiatric diseases is a well-described aspect, that had already been shown in the validation studies and is therefore not surprising [85]. Interestingly, the numbers of outpatient follow-ups and blood draws did not significantly increase in the EVE population, which is likely owing to the generally frequent health encounters experienced by patients with TSC [1, 14, 15].

The observed mean therapy duration of 1210 days (3.3 years) and the retention rates of > 90% for the first year and > 80% for the second and the third years indicated that therapy adherence to EVE was high in the current study, despite the frequently reported tolerability issues. In general, adherence to EVE therapy was higher among adult patients than among children and adolescents with TSC. These findings are in line with a previous retrospective study that reported a retention rate of 98% after 6 months of therapy [58]. As visualised in the Kaplan–Meier survival diagram (Fig. 1), EVE therapy appears most likely to be discontinued within the first months after therapy onset. This early peak of cessation is likely associated with intolerable AEs, similar to previous reports that mTOR therapy discontinuations due to AEs occur most frequently during the first 5 months of therapy [86]. Among children and adolescents with TSC, a notable number of EVE dropouts was reported during the second year of therapy, which can most likely be explained by a lack of effectiveness for the individual case. A lack of reliable evidence exists regarding the optimal length of preventative treatment using EVE or other DMTs in children and adolescents [59]. Moreover, the temporary discontinuation of EVE treatment for medical reasons, such as live vaccinations, must also be considered when evaluating treatments in infants and small children [80].

As with any questionnaire-based survey, this study may suffer from certain methodological limitations that could impact the evaluation and transferability of the results. The potential of selection bias owing to differences in the willingness to participate in studies across different population strata must be considered. Subjective perceptions, and recall bias, particularly regarding the severity of AEs and efficacy, may also influence the analyses in this study. Furthermore, the varying incidence of different TSC manifestations in children vs adult patients as well as a missing approval of EVE for several organ manifestations in early ages may have had an influence on the observed results. As no reliable data were available for possible interactions between EVE and other drugs, this relationship could not be investigated within the scope of the study. Unfortunately, the reporting of laboratory parameters was not sufficient for a statistical evaluation. Moreover, regional or national particularities may have influenced the results; however, the use of established questionnaires and compliance with the STROBE criteria [87] were applied to minimise these aspects to the extent that was reasonably possible.

5 Conclusions

In Germany, EVE is an established DMT for children, adolescents and adults with TSC. The use of EVE typically follows established marketing authorisation guidelines for DRE, SEGA and angiomyolipoma, but off-label use in patients with CRM and neuropsychiatric symptoms was also noted. The effects of EVE, especially for DRE, SEGA and angiomyolipoma, are considerable, and the tolerability appears to be acceptable. It is well known that the treatment of patients with TSC is highly complex and requires close interdisciplinary coordination. In particular, owing to frequent and sometimes severe AEs, which can require dose reductions or the temporary suspension of therapy, regular AE monitoring should be performed. Even if a better access to EVE would be desirable, treatment should be administered by or at least under the guidance of a centre that is experienced in the use and management of mTOR inhibitors in TSC.

Declarations

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Ethics Approval This study received the approval of the local Ethics Committee of Goethe-University, Frankfurt am Main, Germany.

Consent to Participate Informed consent by the patient or legal guardian was mandatory to participate in this study.

Consent for Publication All participants in the study or their legal guardians consented to the publication of the collected data in an anonymised form when they were included in the study.

Availability of Data and Material Anonymised data will be made available on reasonable request, with respect to the German General Data Protection Regulation (Datenschutz-Grundverordnung, DGSVO).

Code Availability Not applicable.

Authors' Contributions LMW, FR, SSB, GKu and AS developed the idea for this analysis. LMW and AS conceived the paper, performed the statistical analysis and wrote the first draft. LMW, FR, SSB, GKu, JPZ, TB, AB, UB, DEF, JG, AH, HH, CH, FH, II, JJ, KMK, KAK, GKl, SK, MK, KM, TM, SM, HM, KMS, FvP, SR, MS, HS, JUS, SSy, CT, RT, AWK, BW, BZ and AS acquired patient data, edited the manuscript and discussed the results. LMW created the charts and figures. All authors contributed to the final manuscript, approved the final manuscript for publication and agree to be accountable for the work presented in the manuscript.

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