NULL HYPOTHESIS CLASS OF EVIDENCE

A randomized controlled trial with everolimus for IQ and autism in tuberous sclerosis complex

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Abstract

Objective

To investigate whether mammalian target of rapamycin inhibitor everolimus can improve intellectual disability, autism, and other neuropsychological deficits in children with tuberous sclerosis complex (TSC).

Methods

In this 12-month, randomized, double-blind, placebo-controlled trial, we attempted to enroll 60 children with TSC and IQ <80, learning disability, special schooling, or autism, aged 4–17 years, without intractable seizures to be assigned to receive everolimus or placebo. Everolimus was titrated to blood trough levels of 5–10 ng/mL. Primary outcome was full-scale IQ; secondary outcomes included autism, neuropsychological functioning, and behavioral problems.

Results

Thirty-two children with TSC were randomized. Intention-to-treat analysis showed no benefit of everolimus on full-scale IQ (treatment effect −5.6 IQ points, 95% confidence interval −12.3 to 1.0). No effect was found on secondary outcomes, including autism and neuropsychological functioning, and questionnaires examining behavioral problems, social functioning, communication skills, executive functioning, sleep, quality of life, and sensory processing. All patients had adverse events. Two patients on everolimus and 2 patients on placebo discontinued treatment due to adverse events.

Conclusions

Everolimus did not improve cognitive functioning, autism, or neuropsychological deficits in children with TSC. The use of everolimus in children with TSC with the aim of improving cognitive function and behavior should not be encouraged in this age group.

Clinicaltrials.gov identifier

NCT01730209.

Classification of evidence

This study provides Class I evidence that for children with TSC, everolimus does not improve intellectual disability, autism, behavioral problems, or other neuropsychological deficits.

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From the ENCORE Expertise Centre for Neurodevelopmental Disorders (I.E.O., A.B.R., S.E.M., K.B.-d.H., L.W.t.H., T.v.d.V., Y.E., H.A.M., M.-C.Y.d.W.) and Departments of Neurology (I.E.O., T.v.d.V., M.-C.Y.d.W.), Child and Adolescent Psychiatry and Psychology (A.B.R., S.E.M., L.W.t.H.), and Pediatrics (K.B.-d.H., H.A.M.), Erasmus MC-Sophia Children's Hospital; Departments of Biostatistics (D.R.) and Neuroscience (Y.E.), Erasmus MC, Rotterdam; and Department of Child Neurology (F.E.J.), Brain Centre Rudolf Magnus, University Medical Centre Utrecht, the Netherlands.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

ADOS = Autism Diagnostic Observation Schedule; **Beery VMI** = Beery-Buktenica Developmental Test of Visual-Motor Integration; **CANTAB** = Cambridge Neuropsychological Test Automated Battery; **CBCL** = Child Behavior Checklist; **CI** = confidence interval; **DSMB** = data safety monitoring board; **IQR** = interquartile range; **mTOR** = mammalian target of rapamycin; **SDSC** = Scale for Children; **SRS** = Social Responsiveness Scale; **TRF** = Teacher Report Form; **TSC** = tuberous sclerosis complex; **WISC-III-NL** = Wechsler Intelligence Scale for Children; **WPPSI-III-NL** = Wechsler Preschool and Primary Scale of Intelligence.

Mutations in the *TSC1* or *TSC2* genes cause constitutive and hyperactivation of mammalian target of rapamycin (mTOR). This is thought to lead to the spectrum of hamartoma growth in tuberous sclerosis complex (TSC).[1] In the brain, cortical malformations result in epilepsy, intellectual disability, autism, or behavioral difficulties in most patients. Currently only supportive care and early seizure control contribute to a better outcome.

The mTOR inhibitor everolimus reduces SEGA or angiomyolipoma volume and seizure frequency in patients with TSC.[2–4] Better epilepsy control can improve cognitive outcome.[4–6] A positive effect of mTOR inhibitors on cognition and behavior in absence of epilepsy has been shown in animal models.[7–10] An open-label study examining sirolimus in TSC-associated lymphangioleiomyomatosis found recall memory improved in 7 of 8 patients.[11] A case series reported improved social interaction in 6 patients.[12] This sparked hope for positive effects on cognition and behavior. However, a recent trial investigating 6 months everolimus treatment in 47 patients found no effect on behavior and development.[13] A randomized trial investigating intractable epilepsy in 23 children with TSC found no effect of sirolimus on neuropsychological outcomes,[14] nor did a study investigating everolimus for SEGA in 24 patients.[15] These studies included limited numbers of patients, and IQ was not a primary outcome, precluding definite conclusions. mTOR hyperactivation has also been implicated in idiopathic autism, sparking a broader interest in mTOR inhibition.

We report on a randomized, placebo-controlled trial examining the effect of 12 months treatment with everolimus on IQ, neuropsychological deficits, and autism in children with TSC.

Methods

Participants

Patients were eligible for inclusion if they had a definite diagnosis of TSC based on the 2012 International Tuberous Sclerosis Complex Diagnostic Criteria,[16] if they were between 4 and 17 years old, and if they had an IQ under 80 or learning disability or special schooling or autism spectrum disorder. Patients were excluded from trial participation if their developmental level was below 3.5 years, if they had more than one epileptic seizure per week, if they had severe liver or kidney dysfunction, or if they were diagnosed with other somatic conditions that required treatment. Patients were also excluded if they had had prior treatment with an mTOR inhibitor.

Data were collected at the ENCORE TSC expertise center at the Erasmus MC–Sophia Children's Hospital in Rotterdam, the Netherlands. Oral and written informed consent was obtained from parents of participating children before randomization, and assent was given by children over 11 years old if they were cognitively able.

Standard protocol approvals, registrations, and patient consents

The trial protocol was approved by the national and Erasmus MC institutional ethics review boards, registration number MEC-2011-483. The trial was performed in agreement with the Declaration of Helsinki (2008) and Good Clinical Practice guidelines. This trial is registered as NCT01730209 at clinicaltrials.gov. An online version of the trial protocol is available at the Erasmus MC website (erasmusmc.nl/encore/Poliklinieken/tubereuze-sclerose-complex/wetenschondtsc/klinondtsc/onderzoeksprotocolC1/?view=active).

Randomization and masking

All participants were randomly assigned (1:1) to receive everolimus or placebo using a permuted-block (block size 4) computer-generated randomization list provided by the Erasmus MC Department of Biostatistics. Randomization was stratified according to age (4–8 years and 9–17 years) and was carried out by the Erasmus MC pharmacy concealing allocation sequence from researchers. All researchers, physicians, parents, and participants were masked to treatment.

Study design

After randomization, patients received masked everolimus or placebo treatment for 12 months. A sample size of 60 participants was calculated to reach 80% power with a 2-sided α of 0.05 to show a minimal treatment effect on the primary outcome of 0.75 SD, which was considered a clinically relevant change.

Patients were contacted after 1 week, 2 weeks, 1 month, and monthly thereafter. At every trial contact, seizure frequency and adverse events were assessed, according to the WHO adverse reaction terminology and the National Cancer Institute common terminology criteria for adverse events version 3.0. Blood was drawn for safety and trough levels at the visits 1 week, 2 weeks, 1 month, 3 months, 6 months, 9 months, and 12 months after the

start of treatment, and 2 weeks after an additional dose change. All trial contacts in between these visits were by telephone.

Placebo and everolimus tablets of 2.5 mg were identical in size, appearance, taste, and odor. Participants received a starting dose of everolimus based on their body surface area, corrected for use of drugs influencing the CYP3A4 enzyme. All other drugs that participants were already taking were continued. Everolimus dose was titrated to trough levels between 5 and 10 ng/mL. To ensure masking, the Erasmus MC pharmacy analyzed all blood samples for trough levels. Patients taking placebo were given simulated trough levels, also requiring occasional dose changes. Administration of everolimus or placebo was once daily, at a fixed time during the day. Tablets were ingested with water. In case of adverse events of grade 2 or higher, everolimus was discontinued until the adverse event subsided or reached grade 1, and was restarted at the last dose without adverse events.

A data safety monitoring board (DSMB) was installed before trial start, consisting of a pediatrician specialized in children with genetic disabilities, a pediatrician specialized in infections, and a statistician. The DSMB was provided biannually with safety reports. The DSMB and Novartis AG were notified within 24 hours in case of a serious event. The DSMB had authority to unmask a participant or to stop the trial in case of safety concerns.

Outcome measures

All outcomes were assessed using the same version of an assessment at baseline and after 12 months for all patients, independent of their age. Primary outcome was change in full-scale IQ, measured at baseline and after 12 months of trial participation using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III-NL)[17] or the Wechsler Intelligence Scale for Children (WISC-III-NL).[18] Scores below the range of the assessment were calculated by hand.

Secondary outcomes measured at baseline and after 12 months of study participation included change in performance IQ and verbal IQ as measured by the Wechsler scales. Other secondary outcomes included change in autistic features measured by the Autism Diagnostic Observation Schedule (ADOS), visual–motor integration measured by the Beery-Buktenica Developmental Test of Visual-Motor Integration (Beery VMI),[19] and fine motor skills by the Grooved Pegboard. Additional secondary outcomes were assessed with the proxy reports of parents, using questionnaires examining (1) behavioral and emotional problems (Child Behavior Checklist [CBCL]), (2) social and communication skills (Social Responsiveness Scale [SRS][20] and Dutch Children's Communication Checklist [CCC-2-NL]),[21] (3) sleep quality (Sleep Disturbance Scale for Children [SDSC]),[22] (4) sensory processing (Short Sensory Profile),[23] and (5) quality of life (Child Health Questionnaire–Parent Form [CHQ-PF50]).[24] Behavioral and emotional problems at school were assessed by teachers of the participants using the Teacher Report Form (TRF).[25] Other outcome measures included frequency of epileptic seizures and safety of everolimus use.

Two instruments were used at baseline, after 6 months, and after 12 months: the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the parental rating scale Behavior Rating Inventory of Executive Functioning.[26] Change in information processing speed, working memory, planning, and attention were examined using the Motor Screening, Big/Little Circle, Stockings of Cambridge, Spatial Span, Spatial Working Memory, and Reaction Time subtests of the CANTAB.

Classification of evidence

Our primary research question was whether everolimus treatment could improve intellectual disability, autism, behavioral problems, and other neuropsychological deficits in children with TSC. This interventional study provides Class I evidence that 12 months of everolimus treatment could not improve full-scale IQ (treatment effect −5.6 IQ points, $p = 0.095$), autism, behavioral problems, or other neuropsychological deficits. Though the sample size of our trial is limited, the observed treatment effect favors the placebo group over the everolimus group, and larger samples as originally intended would not be able to show a positive treatment effect. A beneficial effect of everolimus in very young children is not ruled out.

Statistical analyses

Data from all randomized patients were included in all analyses (intention-to-treat). Endpoint of the trial was defined as 12 months after start of treatment, regardless of completing 12 months of treatment. Baseline categorical data were analyzed using χ^2 tests; baseline numerical data were analyzed using independent samples t tests. The primary and all secondary neuropsychological outcomes were analyzed using a linear regression model, after verifying all assumptions for linear regression. Independent variables included baseline scores, as well as whether the patient was treated with placebo or everolimus. For every outcome measure, test versions were chosen according to age and developmental level of the patient. This caused some patients being assessed using tests without scaled scores for their calendar age. For this reason, raw scores rather than scaled scores were used in the analyses of the Beery-VMI, Grooved Pegboard, SRS, and SDSC, and IQ was calculated by hand for children assessed by WPPSI-III-NL instead of WISC-III-NL. Raw scores for CBCL and TRF were used because standard scores for these questionnaires are truncated. For analyses of raw scores, the age at baseline was included as an independent variable in the linear regression model.

Outcomes examined at 0, 6, and 12 months were first assessed for possible differences between 0 and 12 months. In the case of a statistical difference, analysis was expanded to investigate any statistical differences between 0 and 6 months and between 6 and 12 months.

All data were analyzed using IBM SPSS statistics version 21 (SPSS Inc., Chicago, IL).

Data sharing statement

Individual de-identified participant data from all trial outcomes and the statistical analysis plan will be shared. All participant data will be saved for 15 years after the last patient concluded the last visit (April 2016). Data will be made available to researchers providing a methodologically sound proposal, who will use these data only for this proposal. Interested researchers can inquire at kinderneurologie@erasmusmc.nl. To gain access, data requestors will need to sign a data access agreement.

Results

Between November 21, 2012, and April 28, 2015, 32 patients were randomly assigned to receive everolimus (n = 15) or placebo treatment (n = 17) (figure 1). We aimed to include 60 patients but due to low inclusion rates, we stopped inclusion prematurely without an interim analysis, with consent of the local ethics committee and the DSMB. Baseline characteristics were well-balanced between randomized groups (table 1). Median baseline intelligence was 60 (range 25–107) in patients receiving placebo and 71 (range 22–102) in patients receiving everolimus.

Twelve months of everolimus treatment had no effect on full-scale IQ compared to placebo (treatment effect −5.6 IQ points, 95% confidence interval [CI] −12.3 to 1.0, $p = 0.095$) (figure 2). This lack of benefit from everolimus was similar when analyzing performance IQ (treatment effect −6.4 IQ points, 95% CI −14.1 to 1.3, $p = 0.100$) and verbal IQ (treatment effect −2.9 IQ points, 95% CI −10.9 to 5.2, $p = 0.471$). Analysis of autism features measured by the ADOS showed no benefit of everolimus (treatment effect −0.6, 95% CI −2.0 to 0.9, $p = 0.426$). At baseline, autism spectrum features were found in 11/17 children (65%) treated with placebo, while 12/17 children (71%) showed such features after 12 months of placebo treatment. In children treated with everolimus, 6/15 (40%) showed autism spectrum features at baseline, while after 12 months of treatment such features were present in 7/15 (47%). Everolimus had no effect on visual motor integration as measured by Beery-VMI (treatment effect −1.7, 95% CI −4.2 to 0.9, $p = 0.190$), fine motor skills as measured by the Grooved Pegboard (treatment effect −13.3, 95% CI −45.1 to 18.5, $p = 0.397$), or memory and executive functioning as measured by the CANTAB tasks

Figure 1 Trial profile

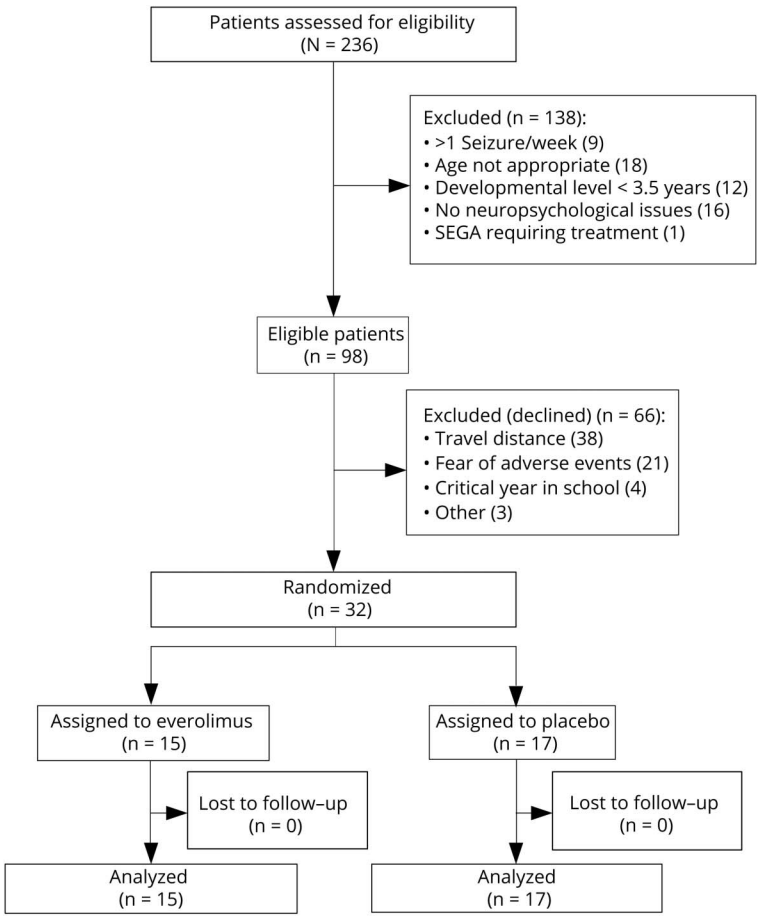


Table 1 Baseline characteristics of included children

	Placebo (n = 17)	Everolimus (n = 15)
Male, n (%)	6 (35)	10 (67)
Age at inclusion, y, median (IQR)	11.5 (6.9–14.9)	12.2 (8.5–14.7)
Mutation *TSC1*/*TSC2*/NMI, n (%)	4/11/2 (24/64/12)	3/10/2 (20/67/13)
History of epilepsy, n (%)	15 (88)	10 (67)
Seizures at inclusion, n (%)	8 (47)	6 (40)
History of infantile spasms, n (%)	5 (29)	2 (13)
Patients taking AEDs at baseline, n (%)	12 (71)	7 (47)
Baseline IQ, median (IQR)	60 (48–79)	71 (60–91)

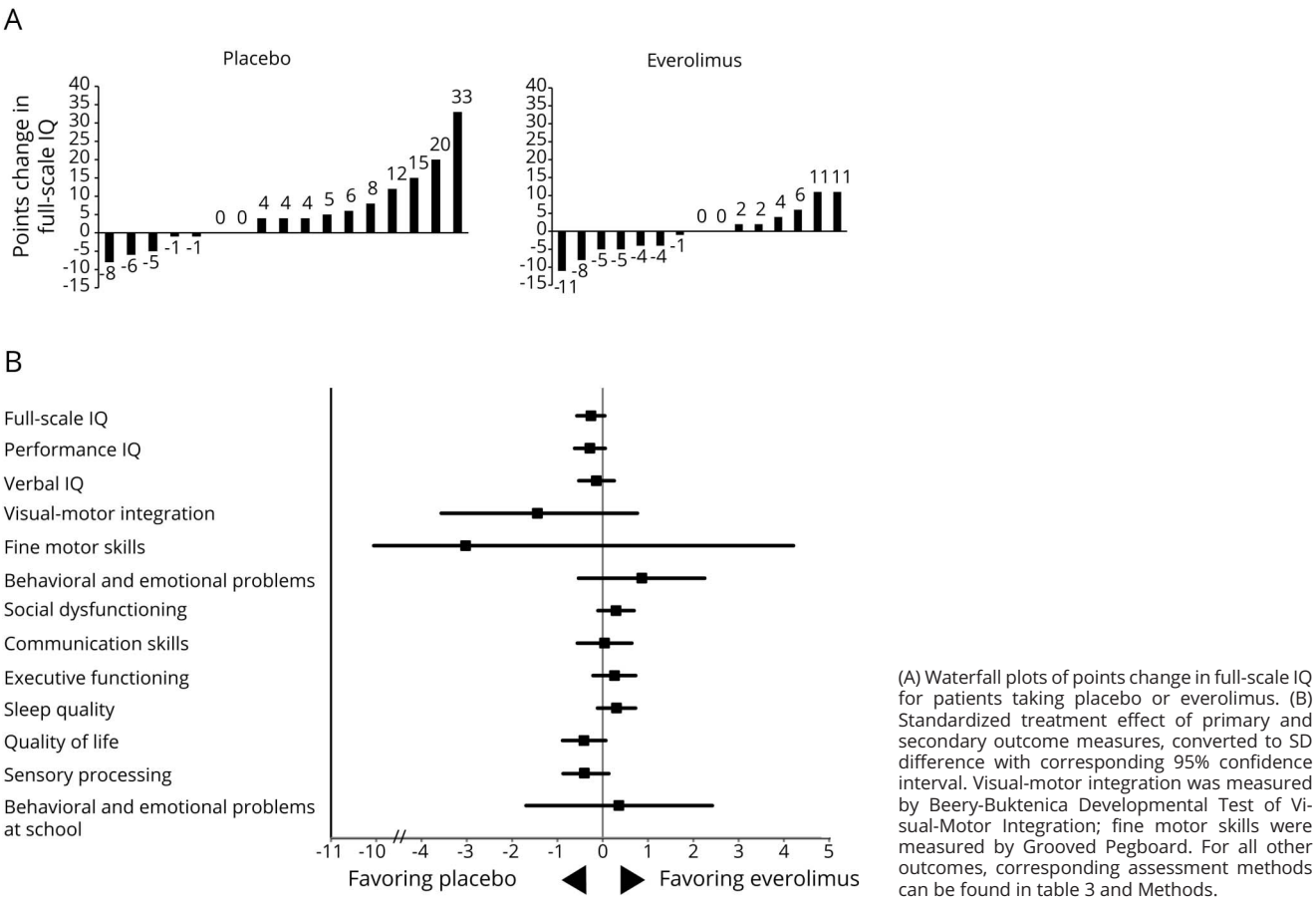
Abbreviations: AED = antiepileptic drugs; IQR = interquartile range; NMI = no mutation identified.
No differences were found between the groups in any of these characteristics ($p > 0.1$).

(table 2). No treatment effect was found on questionnaires examining behavioral and emotional problems at home, social functioning, communication skills, executive functioning, sleep, quality of life, sensory processing, or emotional and behavioral problems at school (table 3).

Epilepsy

As shown in table 1, a total of 25 patients (78%) had a history of epilepsy and 14 patients (44%) still had epilepsy at baseline with a low seizure frequency. In the group taking everolimus, no seizures occurred after long periods of seizure

Figure 2 Treatment effect of everolimus vs placebo on neuropsychological outcomes



(A) Waterfall plots of points change in full-scale IQ for patients taking placebo or everolimus. (B) Standardized treatment effect of primary and secondary outcome measures, converted to SD difference with corresponding 95% confidence interval. Visual-motor integration was measured by Beery-Buktenica Developmental Test of Visual-Motor Integration; fine motor skills were measured by Grooved Pegboard. For all other outcomes, corresponding assessment methods can be found in table 3 and Methods.

Table 2 Cambridge Neuropsychological Test Automated Battery (CANTAB) subtest analyses

CANTAB subtest	Patients analyzed	Treatment effect everolimus vs placebo	95% CI lower bound	95% CI upper bound	*p* Value
MOT motor screening	32	−232.6	−542.9	77.7	0.135
BLC set-shifting	30	1.0	−1.5	3.5	0.414
RTI movement time	21	19.6	−252.7	291.9	0.881
RTI reaction time	21	68.4	−51.6	188.4	0.246
SOC initial thinking time	23	530.2	−1,507.8	2,568.2	0.591
SOC subsequent thinking time	23	282.3	−473.7	1,038.3	0.443
SOC minimum moves	21	0.1	−1.7	1.8	0.915
Short Sensory Profile span length	29	0.1	−0.8	0.9	0.866
SWM between errors	29	−8.9	−27.1	9.3	0.326
SWM strategy	29	0.1	−3.4	3.7	0.946

Abbreviation: CI = confidence interval.
Treatment effect values are unstandardized βs.

freedom. As we purposely included patients with well-controlled epilepsy (no or only incidental seizures), we could not analyze changes in seizure frequency or epilepsy severity.

Everolimus intake

Median everolimus trough level after 6 months of trial participation was 4.7 ng/mL (interquartile range [IQR] 3.9–5.3 ng/mL); median trough level after 12 months was 4 ng/mL (IQR 3.8–6 ng/mL). Median everolimus dose was 5 mg (range 1.25–10 mg). Of the 13 patients receiving everolimus, 9 patients (69%) interrupted treatment due to adverse events, with a median of 2 interruptions per patient, and a median duration of 8 days. Everolimus was taken on 94% of all study days. Of the 15 patients receiving placebo and who completed the treatment period, 4 (27%) interrupted treatment due to adverse events, with a median of 2 episodes, and 2 days per interruption. Placebo was taken on 99% of all trial days.

Adverse events

All patients experienced adverse events (table 4). No grade 3 or 4 adverse events were reported. Infections were more frequent in patients treated with everolimus. One patient

Table 3 Results from all questionnaires

Questionnaire	Feature examined	Treatment effect everolimus vs placebo (95% CI)	*p* Value
Child Behavior Checklist	Behavioral and emotional problems	8.1 (−5.0 to 21.1)	0.215
Social Responsiveness Scale	Social dysfunctioning and autistic features	9.4 (−3.4 to 22.2)	0.144
Dutch Children's Communication Checklist (CCC-2-NL)	Communication skills	0.8 (−10.7 to 12.3)	0.888
Behavior Rating Inventory of Executive Functioning	Executive functioning	2.9 (−2.4 to 8.1)	0.271
Sleep Disturbance Scale for Children	Sleep quality	3.4 (−1.3 to 8.1)	0.143
Child Health Questionnaire–Parent Form (CHQ-PF50)	Quality of life	−4.1 (−8.8 to 0.7)	0.091
Short Sensory Profile	Sensory processing	−0.6 (−1.3 to 0.2)	0.141
Teacher Report Form	Behavioral and emotional problems at school	3.1 (−14.6 to 20.9)	0.715

Treatment effect values are unstandardized βs.

Table 4 All adverse events registered during trial participation

Event	Placebo (n = 17)	Everolimus (n = 15)
Gastrointestinal	12 (71)	14 (93)
Upper respiratory tract infection	13 (76)	12 (80)
Aphthous ulcers	7 (41)	12 (80)
Acne-like skin lesions	9 (53)	10 (67)
Headache	8 (47)	9 (60)
Other infection	5 (29)	9 (60)
Fatigue	8 (47)	8 (53)
Injury due to accident	6 (35)	5 (33)
Eczema	2 (12)	4 (27)
Hemorrhagic disorders	4 (24)	2 (13)
Fever of unknown origin	1 (6)	2 (13)
Edema	1 (6)	2 (13)
Hyperventilation	1 (6)	2 (13)
Anorexia	0	2 (13)
Amenorrhea	0	1 (7)
Worsening of psychiatric symptoms	0	1 (7)
Hypertension	0	1 (7)
Pneumonia	0	1 (7)
Dental cavities	0	1 (7)
Vertigo	2 (12)	0
Osgood-Schlatter disease	1 (6)	0

Values depict n (%) of children who experienced an adverse event. All adverse events were grade 1 or 2. Gastrointestinal adverse events included diarrhea, nausea, vomiting, and constipation. Aphthous ulcers also include stomatitis and mouth ulcers. Other infections included varicella-zoster, measles, and fungal infections. Aphthous ulcers occurred more often in the everolimus group ($p = 0.03$); there was no relationship with dose or blood level. For all other adverse events, differences between the everolimus and placebo group were not significant.

taking everolimus had pneumonia, without requiring hospitalization. Aphthous ulcers occurred in 12 patients (80%) taking everolimus and in 7 patients (41%) taking placebo. Of the 4 patients taking everolimus who had had their menarche at baseline, one patient experienced 2 episodes of amenorrhea, both lasting 5 months. Adverse events resulted in discontinuation of treatment in 4 patients, of whom 2 received everolimus treatment. In the patients taking placebo, in one patient reason for discontinuation was an epileptic seizure after being seizure-free for 6 years, and in the other patient worsening of fatigue. Reasons for discontinuation of everolimus treatment included worsening of psychiatric symptoms in both patients, most importantly depression and aggression.

Discussion

This randomized, double-blind, placebo-controlled trial of everolimus for intelligence, neuropsychological deficits, and autism in children with TSC showed no significant improvement by everolimus treatment on full-scale IQ (treatment effect −5.6 IQ points, 95% CI −12.3 to 1.0, $p = 0.095$). Also, no effect was found on any secondary outcome measure, including performance IQ, verbal IQ, autism as measured by ADOS, and CANTAB tasks examining executive functioning.

Researchers, parents, and patients held much hope for a beneficial effect of everolimus on cognitive function and autism features, as preclinical studies showed significant positive effects on behavior and cognition, and clinical studies showed that everolimus reduces TSC-related tumor growth and seizure frequency in patients. However, our trial shows that, in patients with TSC aged 6.9–14.9 years, everolimus used for 12 months has no beneficial effect on intelligence or autism. These results are in line with a recently published trial that found no benefit of 6 months everolimus treatment in 47 patients with TSC aged 6–21 years on behavior.[13] Since at the time of trial design no previous clinical trials in patients with TSC had been reported with preregistered cognitive assessments as primary outcome, the outcome measures selected in our trial were based on neuropsychological issues reported in literature, and issues signaled by psychiatrists and psychologists with experience in treating patients with TSC. In addition, we used a comprehensive assessment that captures overall functioning of the patients. We chose full-scale IQ as our primary outcome measure because we believe this to be the most clinically relevant outcome for the cognitive functioning of children, as it is a stable outcome measure that covers a broad spectrum of functioning and is predictive of educational success. It might be that full-scale IQ is too broad of a measure to be changed by treatment with a drug for a period of 12 months, so we expanded the assessment battery with a broad range of neuropsychological tests and questionnaires as secondary outcomes. We show no clear sign of improvement in executive functioning, memory, attention, behavior, or autism features. A clinically relevant improvement in cognitive or behavioral measures that was not directly assessed in our trial is unlikely. Due to the nature of the tests, we excluded children under the age of 4, and it might be that in older children IQ is less plastic. With our data, we cannot specifically exclude a positive effect in younger patients.

Our aim was to include 60 patients with TSC to show a clinically relevant treatment effect of 0.75 SD on our primary outcome. Inclusion rate slowed down considerably (we included 2 patients in the last year of the trial), and we decided to discontinue after inclusion of 32 participants. As shown in figure 1, we assessed 98 patients who were eligible for inclusion. Sixty-six (67%) declined participation, mainly due to large travel distance or fear of adverse events. Although we would have preferred to have reached our inclusion goal, our results are robust and show no positive effect. Considering the

high test–retest reliability of our primary outcome measure, we can safely conclude that including 60 patients would not have resulted in a clinically relevant positive effect of everolimus in this age group.

Children randomized to receive everolimus treatment were less likely to have had epilepsy and had slightly higher baseline IQ values (not significant). It could be argued that patients with higher baseline IQ values are less likely to improve. However, it could also be argued that, in children with active epilepsy, it might be more difficult to treat intellectual disability as this is known to be influenced by regular seizures. Our data do not confirm either of these 2 possibilities (not shown).

We decided on a long treatment duration of 12 months. A full year of treatment is a challenge in a clinical trial, but dysfunctional neuropsychological patterns have developed in patients for many years, and the recovery of changes caused by increased mTOR activation is most likely a long-term process. Throughout the trial, we monitored trough levels and compliance. Target trough levels were chosen based on effectiveness in previous trials.[3] The recent registration trial on everolimus for intractable TSC-related epilepsy suggested higher trough levels may be more effective for seizures, and this could also be true for cognition and behavior.[4] However, also in that trial, higher trough levels were difficult to achieve due to adverse events and interactions between drugs. The optimal dose for a possible treatment of cognition and behavior has yet to be defined.

Considering our results, if everolimus could have a positive effect on cognitive and behavioral outcome measures, treatment would most probably need to be initiated in very young patients with TSC when plasticity and developmental speed are at its peak, and mTOR hyperactivation might not yet have caused permanent alterations to the neurodevelopment of the child. Such a window of opportunity for improvement of cognition and behavior might be critical, as shown in animal models of other neurodevelopmental disorders.[27] As we designed our trial to measure IQ, we could not include patients with TSC below the age of 4 years. Future trials investigating the effect of everolimus on intelligence and other neuropsychological outcome measures should consider focusing on this young patient group. Everolimus has been shown to have an antiepileptic effect in TSC, and we know that improved seizure control in young children is a predictor of better cognitive development.[4,6] While treatment with everolimus for seizure control can be worthwhile for young patients for that reason, our results suggest no positive effect of everolimus independent of epilepsy in this particular age group.

We showed that everolimus had no significant effect on intelligence, autism, or neuropsychological functioning in children with TSC aged 4–17 years. This is in line with the results of a recently published study examining the effect of everolimus used for 6 months on neuropsychological deficits in children with TSC. Another ongoing trial investigating adolescents and adults (clinicaltrials.gov NCT01954693) will be of interest as a comparison. We stress that everolimus is a validated treatment for SEGA, and shown to be effective in reducing angiomyolipoma and epilepsy in TSC, but should not be prescribed for a potential improvement of intelligence, autistic features, or neuropsychological functions in children aged 4–17 years.

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Disclosure

I. Overwater, A. Rietman, S. Mous, K. Bindels-de Heus, D. Rizopoulos, L. ten Hoopen, T. van der Vaart, F. Jansen, Y. Elgersma, and H. Moll report no disclosures relevant to the manuscript. M. de Wit reports grants from Sophia Foundation (SSWO), non-financial support from Novartis International AG, and grants from Novartis International AG during the conduct of the study; personal fees from Hoffmann-La Roche; and other from Novartis International AG, outside the submitted work. Go to Neurology.org/N for full disclosures.

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André B. Rietman, MSc	Erasmus MC–Sophia Children's Hospital, Rotterdam, the Netherlands	Author	Contributed to trial design, trial implementation, data collection, statistical analysis, interpretation of the data, and development of the manuscript, approved the final manuscript

Continued

Appendix (continued)

Name	Location	Role	Contribution
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