Safety of Everolimus in Patients Younger than 3 Years of Age: Results from EXIST-1, a Randomized, Controlled Clinical Trial

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Objectives To assess the long-term safety of everolimus in young children with tuberous sclerosis complex (TSC)-associated subependymal giant cell astrocytoma (SEGA).

Study design EXamining everolimus In a Study of Tuberous Sclerosis Complex-1 (EXIST-1) was a multicenter, randomized, double-blind phase 3 study with an open-label extension evaluating the efficacy and tolerability of everolimus in patients with TSC-associated SEGA. Everolimus was initiated at 4.5 mg/m^2/day and titrated to blood trough levels of 5-15 ng/mL. Post hoc analysis of safety data (adverse events [AEs]) was performed in a subgroup of patients aged <3 years at everolimus initiation.

Results Eighteen patients (median age 1.82 years) were included; 16 were still receiving everolimus at the analysis cut-off date of January 11, 2013. Median everolimus exposure was 31.1 months (range, 11.5-39 months). One patient discontinued treatment because of AEs (ie, *Acinetobacter* bacteremia, increased blood alkaline phosphatase, and viral infection). AEs were reported in all patients, but events were mostly grade 1/2 in severity; 12 patients (66.7%) experienced grade 3 events, and 2 patients (11.1%) reported grade 4 events. The most common AEs were stomatitis, cough, pharyngitis, and pyrexia; no new safety issues were identified in this population. Serious AEs were reported in 50% of patients; these were suspected to be medication related in 4 patients (22.2%).

Conclusions Everolimus appears to be a safe therapeutic option for patients aged <3 years with TSC-associated SEGA. The small sample size in this subpopulation limits interpretation of the results; additional studies in the pediatric population are needed and are underway. *(J Pediatr 2016;172:151-5)*.

Trial registration ClinicalTrials.gov: NCT00789828.

Tuberous sclerosis complex (TSC) is a multisystem disorder characterized by the growth of nonmalignant tumors (hamartomas) in various organs.[1] TSC can manifest in utero and affect individuals throughout their lifetime.[2] In the brain, subependymal giant cell astrocytoma (SEGA) occurs in up to 20% of patients with TSC.[3-5] SEGAs typically appear during the first 20 years of life and on occasion have been detected prenatally.[6-9] They are slow-growing tumors composed of astrocytes, spindle cells, and giant cells.[6,10] Although SEGAs are often asymptomatic, their clinical consequences can be grave because of their close proximity to the foramen of Monro. As SEGAs grow, there is the potential for obstruction of cerebrospinal fluid flow, possibly leading to hydrocephalus and increased intracranial pressure, which may result in death.[4,7,11]

Treatment of SEGA includes surgery and pharmacotherapy with mammalian target of rapamycin (mTOR) inhibitors.[12] Surgical resection of SEGA, recommended in patients with acute symptoms,[12] can be curative, but there are risks and a potential for postoperative and long-term complications. Postoperative complications include hemiparesis, development of new seizures, cognitive impairment, hydrocephalus, infections, and even death.[6,7,11,13] In the largest reported series to date of surgically resected SEGAs, including 64 surgeries in 57 patients, complications were most frequent in children aged <3 years than in older patients.[14] Furthermore, if gross total resection is not achieved, there is the potential for SEGA regrowth, necessitating additional surgical interventions and/or therapy.[7,11,13,14]

A multicenter, randomized, double-blind, placebo-controlled phase 3 study, EXamining everolimus In a Study of Tuberous Sclerosis Complex-1 (EXIST-1)

AE	Adverse event
EXIST-1	EXamining everolimus In a Study of Tuberous Sclerosis Complex-1
mTOR	Mammalian target of rapamycin
SAE	Serious AE
SEGA	Subependymal giant cell astrocytoma
TSC	Tuberous sclerosis complex

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(NCT00789828) evaluated everolimus for the treatment of TSC-associated SEGA in 117 patients irrespective of age.[15,16] Short- and long-term evaluation of their therapy is promising.

Everolimus is the only mTOR inhibitor evaluated in a randomized, placebo-controlled clinical trial for patients with TSC and SEGA. It was initially approved for use in patients aged ≥3 years. Data for mTOR inhibitors from other indications in patients aged <3 years are also limited. In TSC, some manifestations are present at birth or soon after,[2] and given the increasing body of evidence that mTOR inhibition may be beneficial not only for SEGA, but also epilepsy, neuropsychiatric problems, skin lesions, and other manifestations,[17-20] a significant number of patients are candidates for medical treatment as infants or toddlers.

Here we report the results of a post hoc analysis focusing on the safety and tolerability of everolimus in the subgroup of EXIST-1 patients aged <3 years when everolimus was initiated, using long-term data with a cut-off date of January 11, 2013.

Methods

The methods used in EXIST-1 have been previously published.[15,16] Patients, irrespective of age, with TSC-associated SEGA and radiologic evidence of ≥1 of 3 conditions (serial SEGA growth, presence of a new SEGA lesion, and/or new or worsening hydrocephalus) were randomly assigned 2:1 to receive double-blinded treatment with either everolimus or placebo. Randomization was stratified by the use of enzyme-inducing antiepileptic medications. Patients received oral everolimus initiated at 4.5 mg/m^2/d (titrated to attain blood trough levels of 5-15 ng/mL) or placebo. Protocol-specified dose modifications were permitted if treatment-related toxic effects occurred.[15,16] In cases of treatment interruption, study medication was resumed if the toxicity recovered to grade ≤1 within 6 weeks. Treatment was generally reintroduced at the initial dose in cases of grade 1-3 toxicity, except with grade 3 stomatitis or pneumonitis, platelets <50 000/mm^3, absolute neutrophil count <500/mm^3, or febrile neutropenia for which treatment was restarted at a lower dose level. The patient was discontinued from the study if treatment was interrupted for ≥6 weeks or if grade 4 toxicity was experienced.

The protocol was approved by the institutional review board/ethics committee at each center, and the study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Safety data were reviewed every 6 months by an independent data-monitoring committee, and all patients provided written informed consent. For participants aged <18 years, written informed consent was obtained from a legally acceptable representative (eg, a parent), and verbal assent was obtained if the patient was able.

The primary efficacy endpoint in the core phase of the study was SEGA response rate (as determined by independent central radiology review). SEGA response was defined as (1) a ≥50% reduction in SEGA volume relative to baseline (where SEGA volume was the sum of all target SEGA lesion volumes identified at baseline); and (2) no unequivocal worsening of nontarget SEGA lesions, no new SEGA lesions (≥1 cm in longest diameter), and no new or worsening hydrocephalus.[15,16] Safety and tolerability were assessed throughout the study according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Rate, severity, and causal relationship of adverse events (AEs) and serious AEs (SAEs) to treatment were recorded. Patients also underwent regular monitoring of hematology, blood clinical chemistry, and urine, as well as regular assessments of vital signs and physical condition.

The core phase of the study was the period lasting from randomization of the first patient until the last randomly assigned patient was treated with everolimus or placebo for 6 months. Because superiority of everolimus was shown during the core treatment phase, a prespecified open-label extension phase was launched wherein all patients, including those originally randomized to receive placebo, who were still in the study at that time or who were being followed up for post-treatment evaluation, were offered the possibility of receiving open-label everolimus.

Statistical Analyses

All analyses are reported for the subset of patients aged <3 years at the time they began receiving everolimus. Numbers and percentages of patients with AEs were summarized. Statistical analyses were performed with SAS software version 9.2 (SAS Institute Inc, Cary, North Carolina).

Results

The EXIST-1 study enrolled 117 patients from 24 centers in 10 countries between August 2009 and September 2010.[15,16] Of these, 78 patients received everolimus and 39 received placebo. The patient flow and disposition are outlined in the **Figure** (available at www.jpeds.com). The overall median patient age at entry into the double-blind phase was 9.5 years (range, 0.8-26.6 years). In total, 111 patients received at least 1 dose of everolimus; 18 patients were aged <3 years at the start of everolimus treatment. Of these 18 patients, 13 (72.2%) were initially randomized to receive everolimus, and 5 (27.8%) were originally randomized to receive placebo but switched to everolimus during the extension phase of the study. At the data cut-off date of January 11, 2013, 16 patients (88.9%) were still receiving everolimus, and 2 (11.1%) had discontinued treatment; 1 patient discontinued because of AEs (*Acinetobacter* bacteremia, increased blood alkaline phosphatase, and viral infection), and the other was lost to follow-up. **Table I** shows the baseline demographics and characteristics of the 18 patients aged <3 years at everolimus initiation. The majority of patients (66.7%) were male, and the median age was 1.82 years (range, 1.1-3.0 years). One-half of the patients (50.0%) had 1 target SEGA lesion, and the other one-half had 2 target lesions. The median sum of