Clinical signs and symptoms have been used to diagnose and define tuberous sclerosis complex (TSC), with the first description being that of the Vogt triad (epilepsy, intellectual disability, and facial angiofibromas). The clinical criteria to diagnose TSC no longer include epilepsy and intellectual disability, and have been further expanded. Presence of a disease-causing mutation in TSC1 or TSC2 (the genes involved in TSC) is now included as an independent diagnostic criterion.

The discovery of the TSC genes has led to knowledge of the TSC proteins (TSC1 or hamartin and TSC2 or tuberin). These proteins inhibit the mechanistic target of rapamycin complex 1 (mTORC1), a critical protein in the mTOR signaling network. If one of the TSC proteins is dysfunctional, the mTOR signaling pathway is hyperactive, resulting ultimately in cellular overgrowth, and giving rise to the many hamartomatous tumors of TSC (e.g., cerebral cortical tubers, angiomylipomas, subependymal nodules, and subependymal giant cell astrocytomas). Inhibitors of mTORC1, such as everolimus and sirolimus, have proven therapeutic benefit for some TSC tumors such as subependymal giant cell astrocytomas and angiomylipomas, and may be beneficial for other TSC lesions. Several reports have supported the notion that mTORC1 inhibitors may benefit individuals with TSC and epilepsy.

Indeed, it has been proposed that mTORC1 inhibitors may truly be antiepileptogenic in this context.

In this issue of Neurology®, Overwater et al. present results from their randomized controlled trial of sirolimus (rapamycin), an inhibitor of the mTOR pathway, for children with TSC and epilepsy. In this study, sponsored by the Dutch Epilepsy Foundation, 12 children were randomized to receive adjunctive sirolimus initially for 6 months, followed by 6 months of standard epilepsy care, and 11 children received standard care followed by 6 months of adjunctive sirolimus. In this intention-to-treat analysis, there was no therapeutic benefit of sirolimus on seizure frequency.

Although this study provides Class III evidence in support of their result, the authors point out that “The study lacked the precision to exclude a benefit from sirolimus.” The investigators further note that the sample size is small, and all children were not able to reach the sirolimus target trough blood concentration. Additionally, 3 children became seizure-free during the sirolimus treatment phase, leading the authors to suggest that sirolimus may be beneficial for some children. Seizure freedom in this particularly refractory epilepsy population is remarkable.

The authors have included in the supplementary material a useful comprehensive table summarizing the literature (case studies and case reports with references) on mTORC1 inhibitor treatment for epilepsy in TSC. They included 3 reports on sirolimus and 10 reports on everolimus. As the current study was not able to rule out a beneficial effect, the authors call for further studies to assess the value of mTORC1 inhibitors in TSC-related epilepsy.

One consideration is that there may be differential efficacy between everolimus and sirolimus. French et al. reported at the 2016 annual meeting of the American Academy of Neurology in Vancouver, Canada, on the clinically meaningful and significant reduction in seizure frequency in a randomized placebo-controlled trial of adjunctive everolimus in 366 patients with TSC and epilepsy. A full report on this trial is pending; peer review will provide confidence in the findings. Safety and adverse effects reporting will help determine effectiveness for these medications.

Overwater and coauthors are to be commended for their careful and diligent study. It is important for patients with TSC, their families, and their health care providers to be aware of both the negative and positive information regarding epilepsy treatment to enhance their decisions regarding optimal therapies for one of the most significant health challenges in TSC. We await the final results of current studies, and those of future studies, to inform evidence-based decisions about the use of this drug class in the challenging setting of seizures related to TSC.
STUDY FUNDING
No targeted funding reported.

DISCLOSURE
The author’s hospital has received research funds from Novartis related to research conducted with everolimus. He was a site principal investigator for the EXIST 3 trial (mentioned in this editorial). He has received honoraria for speaking and consulting from Novartis. Go to Neurology.org for full disclosures.

REFERENCES