DOI:10.4274/tnd.78466
Turk J Neurol 2018;24:193-194

Adjunctive Everolimus Therapy for Treatment-resistant Focal-onset Seizures Associated with Tuberous Sclerosis: A Phase 3, Randomised, Double-blind, Placebo-controlled Study

Tüberoskleroz ile İlişkili, Tedaviye Dirençli Fokal Başlangıçlı Nöbetler için Yardımcı Everolimus Tedavisi: 3 Aşamalı, Randomize, Çift Kör, Plasebo Kontrollü Çalışma

Mustafa Karaoğlan

Istanbul Sultan Abdulhamid Han Training and Research Hospital, Clinic of Neurology, Istanbul, Turkey

Keywords: Evorolimus, focal epilepsy, tuberosclerosis
Anahtar Kelimeler: Everolimus, fokal epilepsi, tüberoskleroz

Adjunctive Everolimus Therapy for Treatment-resistant Focal-onset Seizures Associated with Tuberous Sclerosis: A Phase 3, Randomised, Double-blind, Placebo-controlled Study

Epilepsy is the most common neurologic symptom of tuberous sclerosis complex, an autosomal dominant genetic disorder, and is reported in 85% of patients with the condition. Untreated early-onset epilepsy is associated with an increased risk of neurodevelopmental disabilities, including autism spectrum disorder and intellectual disability. To date, tuberous sclerosis complex is treated symptomatically with antiepileptic drugs, which are not specific for the underlying cause. Antiepileptic drugs can be particularly effective for some specific seizure types or epilepsy syndromes. However, these antiepileptic drugs are specifically developed for a particular molecular pathophysiology.

Everolimus is a mammalian target of the rapamycin (mTOR) inhibitor that has been approved for the treatment of subependymal giant-cell astrocytoma and renal angiomyolipoma in patients with tuberous sclerosis complex. Everolimus, an mTOR inhibitor, has been used for various benign tumors associated with tuberous sclerosis complex. French et al. (1) assessed the efficacy and safety of two trough exposure concentrations of everolimus, 3-7 ng/mL (low exposure) and 9-15 ng/mL (high exposure), compared with placebo as an adjunctive therapy for treatment-resistant focal-onset seizures in tuberous sclerosis complex. This study aimed to understand whether everolimus could control seizures by targeting specific molecular defects in patients with tuberous sclerosis complex and treatment-resistant focal epilepsy.

In this phase 3, randomized, double-blind, placebo-controlled study, patients aged 2-65 years with tuberous sclerosis complex and treatment-resistant seizures receiving one to three concomitant antiepileptic drugs were included. Ninety-nine centers across 25 countries participated in the study. Participants were randomly assigned (1:1:1), via permuted-block randomization implemented by "Interactive Response Technology" software, to receive placebo, low-exposure everolimus, or high-exposure everolimus. Patients, investigators, site personnel, and the sponsor's study team were blinded to treatment allocation. The starting dose of everolimus depended on age, body-surface area, and concomitant use of cytochrome 3A4/P-glycoprotein inducers. Dose adjustments were made to attain target trough ranges during a 6-week titration period, and as needed during a 12-week maintenance period of core phase. Patients or their caregivers recorded events in a seizure diary throughout the study. The primary endpoint was the change from baseline in the frequency of seizures during the maintenance period, defined as response rate and median percentage reduction in seizure frequency, in all patients.

Three hundred sixty-six patients were enrolled in the study. Patients were randomized into 3 different groups, as placebo

Address for Correspondence/Yazışma Adresi: Mustafa Karaoğlan MD, Istanbul Sultan Abdulhamid Han Training and Research Hospital, Clinic of Neurology, Istanbul, Turkey
Phone: +90 541 443 77 03 E-mail: mkaraoglan@gmail.com ORCID ID: orcid.org/0000-0001-9420-2663
Received/Geliş Tarihi: 09.10.2017 **Accepted/Kabul Tarihi:** 05.12.2017

(n=119), low-exposure everolimus (n=117) or high-exposure everolimus (n=130). The response rate was 15.1% with placebo (95% CI: 9.2-22.8; 18 patients) compared with 28.2% for low-exposure everolimus (95% CI: 20.3-37.3; 33 patients; p=0.008) and 40.0% for high-exposure everolimus (95% CI: 31.5-49.0; 52 patients; p<0.0001). The median percentage reduction in seizure frequency was 15% (95% CI: 0.1-21.7) with placebo versus 29.3% with low-exposure everolimus (95% CI: 18.8-41.9; p=0.003) and 39.6% with high-exposure everolimus (95% CI: 35.0-48.7; p<0.0001). Grade 3 or 4 adverse events occurred in 13 (11%) patients in the placebo group, 21 (18%) in the low-exposure group, and 31 (24%) in the high-exposure group. Serious adverse events were reported in three (3%) patients who received placebo, 16 (14%) who received low-exposure everolimus, and 18 (14%) who received high-exposure everolimus. Adverse events led to treatment discontinuation in two (2%) patients in the placebo group versus six (5%) in the low-exposure group and four (3%) in the high-exposure group.

In conclusion, this study demonstrates that everolimus is effective in the treatment of epileptic seizures in patients with tuberous sclerosis complex. Everolimus, a disease-modifying drug targeting the underlying molecular pathology of tuberous sclerosis complex, represents a new treatment option for patients with treatment-resistant seizures associated with tuberous sclerosis complex.

Reference

1. French JA, Lawson JA, Yapici Z, Ikeda H, Polster T, Nabbout R, Curatolo P, de Vries PJ, Dlugos DJ, Berkowitz N, Voi M, Peyrard S, Pelov D, Franz DN. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. Lancet 2016;388:2153-2163.