



Zonisamide Should Be Considered a First-Line Antiepileptic Drug for Patients with Newly Diagnosed Partial Epilepsy

Efficacy and Tolerability of Zonisamide Versus Controlled-Release Carbamazepine for Newly Diagnosed Partial Epilepsy: A Phase 3, Randomised, Double-Blind, Non-Inferiority Trial.

Baulac M, Brodie MJ, Patten A, Segieth J, Giorgi L. *Lancet Neurol* 2012;11:579–588.

BACKGROUND: Additional options are needed for monotherapy treatment of adults newly diagnosed with partial epilepsy. This trial compares the efficacy and tolerability of once-daily zonisamide with twice-daily controlled-release carbamazepine monotherapy for such patients. **METHODS:** In this phase 3, randomised, double-blind, parallel-group, non-inferiority trial, adults from 120 centres in Asia, Australia, and Europe, aged 18–75 years and newly diagnosed with partial epilepsy, were randomly assigned (in a 1:1 ratio, done with a computer-generated pseudorandom code) to receive zonisamide or carbamazepine. Patients, investigators, and sponsor personnel giving drugs, analysing outcomes, and interpreting data were masked to treatment allocation. After treatment initiation (zonisamide 100 mg/day vs carbamazepine 200 mg/day [given in two doses]) and up-titration (to 300 mg/day vs 600 mg/day), patients entered a 26–78 weeks flexible-dosing period (200–500 mg/day vs 400–1200 mg/day, according to response and tolerance). Once patients were seizure-free for 26 weeks they entered a 26-week maintenance phase. The primary endpoint was the proportion of patients who achieved seizure freedom for 26 weeks or more in the per-protocol population. This trial is registered with ClinicalTrials.gov, number NCT00477295. **FINDINGS:** Five hundred eighty-three patients were randomly assigned to treatment groups (282 zonisamide, 301 carbamazepine), of whom 456 were analysed for the primary endpoint (per-protocol population: 223 zonisamide, 233 carbamazepine). 177 of 223 (79.4%) patients in the zonisamide group and 195 of 233 (83.7%) patients in the carbamazepine group were seizure-free for 26 weeks or more (adjusted absolute treatment difference -4.5%, 95% CI -12.2 to 3.1). The incidence of treatment-emergent adverse events was 170 (60%) in the zonisamide group versus 185 (62%) in the carbamazepine group, of which 15 (5%) versus 17 (6%) were serious and 31 (11%) versus 35 (12%) led to withdrawal. **INTERPRETATION:** Zonisamide was non-inferior to controlled-release carbamazepine—according to International League Against Epilepsy guidelines—and could be useful as an initial monotherapy for patients newly diagnosed with partial epilepsy.

Commentary

Currently, antiepileptic drugs (AEDs) used for the treatment of partial seizures are initially approved as add-on therapy. The clinical trials are designed to recruit subjects with pharmacoresistant epilepsy. It is more difficult to address and consider whether individual AEDs could be used as therapy for patients with newly diagnosed partial epilepsy. Studies suggest that there is no significant difference among efficacy of first-line AEDs when treating partial seizures (1, 2). The International League Against Epilepsy (ILAE) developed guidelines for the development of well-designed clinical trials aimed to investigate the effectiveness of individual AEDs as treatment for patients with newly diagnosed epilepsy (3). These guidelines

recommended randomized active controlled trials with clearly defined primary outcome variables, a minimum duration of 48 weeks, without forced exit criteria, and information on the proportion of patients who were seizure free for 24 weeks or more. For non-inferiority trials, the sample size must be large enough to show non-inferiority with a $\leq 20\%$ relative difference between treatment arms based on 80% power in a non-inferiority analysis versus an acceptable comparator. Using these guidelines, three trials have been completed: levetiracetam versus carbamazepine (4), pregabalin versus lamotrigine (5), and the most recent study, zonisamide versus carbamazepine (6).

Baulac and colleagues report on the results of the zonisamide versus carbamazepine randomized, double-blind, non-inferiority monotherapy trial among subjects with newly diagnosed partial epilepsy (6). Zonisamide is an AED with multiple mechanisms of action including inhibition of Na^+ channels and reduction of T-type Ca^{2+} currents. It is licensed

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in multiple countries for the treatment of partial seizures as adjunctive therapy. Carbamazepine is commonly used as a comparator in monotherapy trials. Subjects were patients with newly diagnosed partial or localization-related epilepsy recruited throughout Asia, Australia, and Europe. Subjects with primary generalized epilepsy were excluded. Subjects with unclassified generalized tonic clonic seizures were included. The target dose for zonisamide was 300 mg per day and for carbamazepine was 600 mg per day in divided doses. After a 4-week titration period, subjects were followed for a flexible dosing period of 26–78 weeks. The primary endpoint was the proportion of patients achieving seizure freedom for 26 weeks while receiving a stable dose of medication. The analyses were done using logistic regression, adjusted for country group, and done using the per protocol population (subjects in the intention to treat population who had no major protocol violations or deviations).

The total number of subjects enrolled in the trial were 583 (282 randomized to receive zonisamide and 301 to carbamazepine). For the primary endpoint analysis using the per protocol population, 223 were treated with zonisamide and 233 received carbamazepine. There were no significant differences in demographic characteristics between the groups. Among the zonisamide group, 79.4% were seizure free; among the carbamazepine group, 83.7% were seizure free. After adjusting for country group, the absolute treatment difference was -4.5% with a 95% confidence interval of -12.2 to 3.1. The lower limit of -12.2 exceeded the ILAE prespecified margin of -12% by a small amount. The relative treatment difference was -5.4% with a 95% confidence interval of -14.7 to 3.7. The lower limit of -14.7 is above the ILAE preset -20%. When looking at the number of subjects who were seizure free for 52 weeks, the percentages were similar (67.6 % for zonisamide group and 74.7% for carbamazepine group).

There were no unexpected safety findings. One timely exclusion was those with HLA-B*1502 allele. This exclusion may explain why there were no reported cases of Stevens–Johnson syndrome or toxic epidermal necrolysis. The most frequently reported treatment-emergent adverse events were headache, decreased appetite, somnolence, dizziness, and weight loss. Not surprisingly, decreased appetite and weight loss were common in the zonisamide group whereas dizziness was more common in the carbamazepine group. Serious treatment-emergent adverse events were reported in 32 patients, with 10 considered to be possibly or probably treatment related.

This well-designed and controlled multinational randomized non-inferiority study supports the use of zonisamide as first-line therapy for the treatment of partial seizures. The study design used the ILAE guidelines for non-inferiority trials with well-defined limits of non-inferiority and an effective active comparator. The results of this trial impact the treatment of persons with epilepsy; without monotherapy trials, there is limited evidence to support monotherapy use of many currently available AEDs, particularly in patients with newly diagnosed epilepsy.

by Alison M. Pack, MD, MPH

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