Seizure 55 (2018) 17–24

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Unblinded, randomized multicenter trial comparing lamotrigine and valproate combination with controlled-release carbamazepine monotherapy as initial drug regimen in untreated epilepsy

Byung In Lee[a,h,*], Soon Kee No[b], Sang-Doe Yi[c], Hyang Woon Lee[d], Ok Joon Kim[e], Sang Ho Kim[f], Myeong Kyu Kim[g], Sung Eun Kim[h], Yo Sik Kim[i], Jae Moon Kim[j], Se-Jin Lee[k], Dong Jin Shin[l], Sung Pa Park[m], Yeong In Kim[n], Kyoung Heo[a], Yong Won Cho[c], Yang-Je Cho[a], Youn Nam Kim[o]

[a] Department of Neurology, Yonsei University College of Medicine, Seoul, Korea
[b] Department of Neurology, Bong Seng Memorial Hospital, Busan, Korea
[c] Department of Neurology, Keimyung University School of Medicine, Daegu, Korea
[d] Department of Neurology, Ewha Womans University School of Medicine, Seoul, Korea
[e] Department of Neurology, CHA University, Seongnam, Korea
[f] Department of Neurology, Dong-A University College of Medicine, Busan, Korea
[g] Department of Neurology, Chonnam National University Medical School, Gwangju, Korea
[h] Department of Neurology, Inje University College of Medicine, Busan, Korea
[i] Department of Neurology, Wonkwang University School of Medicine, Iksan, Korea
[j] Department of Neurology, Chungnam National University School of Medicine, Daejeon, Korea
[k] Department of Neurology, Yeungnam University College of Medicine, Daegu, Korea
[l] Department of Neurology, Gachon University Medical Center, Incheon, Korea
[m] Department of Neurology, Kyungpook National University School of Medicine, Daegu, Korea
[n] Department of Neurology, The Catholic University of Korea College of Medicine, Seoul, Korea
[o] Clinical Trial Center, Yonsei University Health System, Severance Hospital, Seoul, Korea

ARTICLE INFO

Article history:
Received 20 October 2017
Received in revised form 26 December 2017
Accepted 28 December 2017
Available online xxx

Keywords:
Monotherapy
Combination therapy
CBZ-CR
LTG + VPA
Initial drug regimen

ABSTRACT

Purpose: To compare controlled-release carbamazepine monotherapy (CBZ-CR) with lamotrigine and valproate combination therapy (LTG + VPA) in equivalent total drug load, as initial drug regimen in untreated patients with partial and/or generalized tonic-clonic seizures (GTCS).
Methods: This unblinded, randomized, 60-week superiority trial recruited patients having two or more unprovoked seizures with at least one seizure during previous three months. After randomization into CBZ-CR or LTG + VPA, patients entered into eight-week titration phase (TP), followed by 52-week maintenance phase (MP). Median doses of CBZ-CR and LTG + VPA were 600 mg/day and 75 mg/day + 500 mg/day, respectively. Primary outcome measure was completion rate (CR), a proportion of patients who have completed the 60-week study as planned. Secondary efficacy measures included seizure-free rate (SFR) for 52-week of MP and time to first seizure (TTFS) during MP.
Results: Among 207 randomized patients, 202 underwent outcome analysis (104 in CBZ-CR, 98 in LTG + VPA). CR was 62.5% in CBZ-CR and 65.3% in LTG + VPA ($p = 0.678$). SFR during MP was higher in LTG + VPA (64.1%) than CBZ-CR (47.8%) ($P = 0.034$). TTFS was shorter with CBZ-CR ($p = 0.041$). Incidence of adverse effects (AEs) were 57.7% in CBZ-CR and 60.2% in LTG + VPA and premature drug withdrawal rates due to AEs were 12.5% and 7.1%, respectively, which were not significantly different.
Conclusion: CR was comparable between LTG + VPA and CBZ-CR, however, both SFR for 52-week MP and TTFS during MP were in favor of LTG + VPA than CBZ-CR. The study suggested that LTG + VPA can be an option as initial drug regimen for untreated patients with partial seizures and/or GTCS except for women of reproductive age.

* Corresponding author at: Department of Neurology, Inje University Haeundae Paik Hospital, 875 Haeundae-ro, Haeundae-gu, Busan, 48108, Korea.
E-mail address: bilee@paik.ac.kr (B.I. Lee).

https://doi.org/10.1016/j.seizure.2017.12.008
1059-1311/

1. Introduction

Long-term observational studies [1–3] illuminated outcomes of antiepileptic drug (AED) therapy in epilepsy. Prolonged seizure control is achieved in 47% of patients by the first drug and in another 13% by the second drug trial [1]. Those patients who failed to adequate trials of first two drug regimens respond poorly to further drug trials to fulfill the criteria of drug resistant epilepsies (DRE) [4]. Therefore, optimization of first drug regimen seems quite critical to achieve better outcome of long-term pharmacotherapy of epilepsy [5].

Initial monotherapy is the rule in pharmacotherapy of untreated epilepsy. Sixteen new AEDs have been introduced to the market until recently, however, none of them were found superior to controlled release form of carbamazepine (CBZ-CR) in randomized clinical trials (RCTs) of initial monotherapy in patients with newly diagnosed partial seizures and/or generalized tonic-clonic seizures (GTCS) [6]. Therefore, any further improvement in the outcome of initial monotherapy than CBZ-CR monotherapy is unlikely to be achieved with currently available 25 AEDs.

Monotherapy vs. Polytherapy has been the subject of endless debates among epileptologists, primarily due to lack of evidence indicating any differences in outcome [7]. Previous comparative studies of substitution monotherapy and combination therapy in patients who failed to monotherapy failed to show any significant differences [8,9]. However, Kwan and Brodie [9] indicated that the combination of two drugs, one having multiple mechanisms of action (MOA) and the other having sodium-channel blocking effects, carried significantly superior efficacy to other combinations, which has raised interests for mechanistic combinations of drugs for synergistic pharmacodynamic interactions. Preclinical studies using isobolographic analysis have provided ample evidence of synergistic interactions of AEDs having different MOA but either additive or infra-additive interactions of AEDs having similar MOA [10]. Clinical experiences also support the preclinical data of mechanistic combinations. Combination of AEDs having different MOA, such as LTG and valproate (VPA) [11], ethosuximide and VPA [12], LTG and topiramate [13], were shown to have synergistic interactions, while combining AEDs having sodium-channel blocking actions were associated with poorer outcomes [14]. Among various drug regimen, combination of LTG and VPA (LTG + VPA) was subjected to intense clinical assessments [15–17] and their synergistic interactions are widely accepted among clinicians [18,19].

A fair comparison of monotherapy and combination therapy requires balanced baseline patient characteristics, appropriate dose-titration schedules including initial target dose (ITD), equivalent total drug load (TDL) between two groups, as well as appropriate selection of drugs for combination, preferably consisting of drugs carrying synergistic interactions. These requirements are difficult to meet in trials of patients who failed to previous AEDs therapy but feasible in newly diagnosed patients. Decker et al. [20] conducted a study comparing CBZ monotherapy with combination therapy of CBZ and VPA as initial treatment in patients with untreated epilepsy, which was the only RCT comparing monotherapy with combination therapy in equivalent TDL. Outcome measures were numerically in favor of combination therapy, but differences were not statistically significant. Criticisms against the study include that combination of CBZ and VPA has significant pharmacokinetic drug interactions and no proven synergistic interactions. More importantly, the study is considered not practical because we don't need combination therapy as initial drug regimen. However, if combination therapy was considered to provide a potential benefit in certain specific clinical scenarios, comparative trials of monotherapy and combination therapy as initial drug regimen may be justifiable under the concept of individual patient-oriented optimal pharmacotherapy of epilepsy.

We chose LTG + VPA as the comparator of CBZ-CR monotherapy in initial treatment of patients with untreated partial seizures (PS) and/or generalized tonic-clonic seizures (GTCS).

2. Methods

The study was conducted at 14 centers in Korea in accordance with Good Clinical Practice Guidelines. An independent ethics committee at each participating center approved the protocol before the commencement of patient's enrollment. All participants provided written informed consent before entering the study.

2.1. Patients

Both inclusion and exclusion criteria were summarized in the appendices (Table A.1).

Patients aged $\geq$ 16 years with newly diagnosed or untreated partial onset seizures and/or GTCS only were eligible, whereas women who were planning to be pregnant or not using appropriate contraceptive measures were not eligible. Patients with history of absence seizures or myoclonic seizures were excluded. Seizure types and epilepsy syndromes were diagnosed according to the ILAE Classification System [21,22]. Patients should have experienced two or more seizures separated by at least 24 h with occurrence of at least one seizure during previous three months. All patients undertook both EEG and MRI before randomization. Patients were included to the study if they were either newly diagnosed or untreated for at least 12 months before the index seizure (the last seizure episode precipitated their inclusion to the study). Patients who had short-term AEDs treatment ($\leq$ 2 weeks) only with or without emergency rescue treatment (with either benzodiazepines or other AEDs) was allowed on the assumption that a short-term AEDs therapy may not alter the natural course or responsiveness to AEDs therapy of their illnesses.

2.2. Study design

Dose-titration schedules are summarized in the appendices (Fig. A.1). After one-week screening period, patients were randomly assigned to enter eight-week titration phase (TP) during which they received either CBZ-CR 100 mg/day or LTG 25 mg/day for the first two weeks. At third week, CBZ-CR was increased to 200 mg/day in two divided doses or LTG to 50 mg once a day, which was further increased to CBZ-CR 400 mg/day in divided doses or LTG 75 mg once a day during the next two weeks. At 7th week of TP, CBZ-CR was further increased to 600 mg/day in two divided doses, while VPA 500 mg was added to LTG 75 mg in once a day dosing, which were the ITD of study drugs. During 52-week of maintenance phase (MP), patients were followed at clinic every 4-week interval and caring physicians were allowed to escalate the dose of study drugs if patients had experienced seizure recurrences (including aura only) during previous month. Maximum dose of CBZ-CR was 1200 mg/day and LTG was 200 mg/day. Dose escalation of CBZ-CR was made by 200 mg at 4-week interval whereas LTG was first increased to 100 mg/day and then by 50 mg at 4-week interval. VPA was fixed at 500 mg/day throughout MP. In cases developing tolerability problems, CBZ-CR or LTG was decreased to the dose at previous clinic visit. Minimal allowable doses throughout MP were CBZ-CR 400 mg/day or LTG 50 mg/day and VPA 500 mg/day.