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

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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.

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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.

2.3. Assessment

All patients recorded their seizures and AEs using daily records. Although auras or simple partial seizures of subjective symptoms were considered as a basis for dose-escalation of study drugs, only simple partial motor seizures were included to the seizure count as complex partial seizures (CPS) and GTCS. Investigators were keen to the presence or absence of awareness during and after the event for differential diagnosis of complex partial seizures from simple partial seizures. AEs were assessed at each visit through nonstructured interviews. Blood samples were collected for measurements of complete blood cell count and chemistry. Blood levels of study drugs were not measured. Compliance was assessed on the basis of patients' daily record and counting returned pills at each visit. Poor-compliance was defined as pill consumption less than 80% of the prescribed amount at each visit.

2.4. Outcome measures

The primary outcome measure was completion rate (CR), the proportion of patients who has completed the 60-week study (8-week TP and 52-week MP) as planned. Secondary efficacy measures included (1) SFR during the entire 52-week MP and (2) Time to first seizure (TTFS) from the start of MP. Tolerability measures included incidences of AEs and premature withdrawal rate from study due to AEs. Quality of life (QOL) was measured by QoLIE-31, administered at the beginning and the end of study.

2.5. Statistical analysis

There were no comparative trials of CBZ-CR monotherapy and LTG + VPA combination therapy. Since the Guideline by ILAE in 1998 regarded 20% difference as the minimum outcome difference being clinically important [23], we empirically chose CR of 70% in LTG + VPA and 50% for CBZ-CR to calculate the sample size of this study. A sample size of 94 per group was required to achieve 80% power with a two-tailed significance level of 0.05. Considering a dropout rate of 15%, we planned to recruit 110 patients per group. Randomization was performed using a block randomization to ensure equal numbers of subjects in each study group at each center. The groups were compared using either Student's *t*-test or chi-square test. The primary outcome was tested by chi-square test, and Kaplan-Meier method was used for secondary outcomes. A log-rank test was used for the group comparisons, and hazard ratios were estimated using the Cox proportional hazards model. Mixed model analysis was performed for the comparison of QoLIE-31 at the beginning and the end of study. Two-tailed values of $p < 0.05$ were considered statistically significant. All analyses were performed with SAS software, ver. 9.2 (SAS Institute Inc.). Data were analyzed according to the intention-to-treat (ITT) principle.

3. Results

3.1. Study progression

Patient recruitment began in July 2008 at 14 centers in Korea and finished in September 2011. A total of 207 patients were recruited to the study and randomized, which was a little less than that of the original plan (n = 220). However, 202 of 207 patients who were randomized took at least one dose of study drugs and subjected to data analysis sets (104 in CBZ-CR and 98 in LTG + VPA), which was more than the target number of patients required for the analysis (n = 94 per group). The study progression was illustrated in Fig. 1. Thirty-four patients were dropped out prematurely during TP, 14 in CBZ-CR [AEs in 8, lack of efficacy (LOE) in 1, others in 5] and 20 in LTG + VPA [non-compliance (NC) in

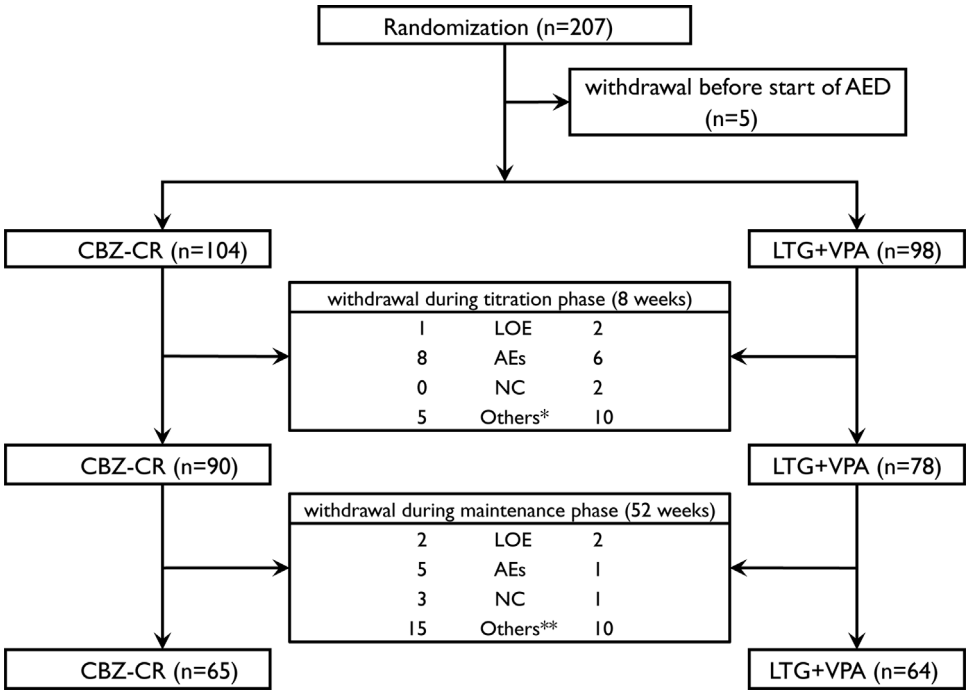

Fig. 1. A diagram of study progression.
Among 202 patients who received the study medications, 34 patients were dropped out prematurely during titration and 39 patients during maintenance phase.
CBZ-CR, controlled release-carbamazepine; LTG + VPA, combination of lamotrigine and valproate; LOE, lack of efficacy, AEs, adverse events; NC, non-compliance.
Others*; other causes of study drug withdrawal during titration phase (TP), which included withdrawal of consents in 4 patients and missed follow-up visit in 1 patient in CBZ-CR, whereas protocol violation in 2 patients, withdrawal of consent in 6 patients, and missed follow-up visit in 2 patients in LTG + VPA.
Others**; other causes of study drug withdrawal during maintenance phase (MP), which included withdrawal of consent in 11 patients and missed follow-up visit in 4 patients in CBZ-CR, whereas protocol violation in 1 patient, withdrawal of consent in 5 patients, and missed follow-visit in 4 patients in LTG + VPA.

2, LOE in 2, AEs in 6, others in 10]. During 52-week of MP, 25 patients from CBZ-CR and 14 patients from LTG + VPA were dropped out. Adherence rates to study drugs ranged from 93.9% to100% (mean = 96.9%) in CBZ-CR and 91.5% to100% (mean = 98.9%) in LTG + VPA, which were not significantly different (p = 0.09).

3.2. Patient demographics

Demographic and clinical characteristics were not different between two groups (Table 1). Etiology of epilepsy was unknown in approximately two-thirds of patients. MRI-lesions were found in 29 of CBZ-CR and 23 of LTG + VPA, with focal tissue loss being the most frequent (11 and 7, respectively), followed by hippocampal sclerosis (7 and 5, respectively) and focal cortical dysplasia (5 and 4, respectively). Among 104 patients assigned to CBZ-CR, 80 were never treated, 14 had short-term treatment ($\leq$ 2 weeks) only with or without emergency rescue treatment, and 10 had prior history of AEDs therapy, which were 73, 12, and 13 patients in LTG + VPA, respectively. Among those assigned to CBZ-CR, 89 patients were diagnosed as localization-related epilepsy (LRE) and 15 patients were undetermined epilepsy (UE), which were 78 patients and 20 patients in LTG + VPA, respectively. Among 35 patients classified into UE, six patients (3 patients in each group) showed generalized spikes or spikes and waves in EEG and normal MRI but their semiology described clear focal features consisting of visual auras (2), somatosensory aura (1), psychic aura (1), spatial disorientation (2), and additional focal motor symptoms in one patient. Remaining 29 patients did have either nocturnal Grand Mal seizures or GTCS without focal features and revealed no specific abnormalities in EEG and MRI. Mean number of seizures during previous six months was 8.8 episodes in CBZ-CR and 8.6 episodes in LTG + VPA with median seizure numbers of 2 in each group.

3.3. Outcome measures

Sixty-five patients (62.5%) in CBZ-CR and 64 patients (65.3%) in LTG + VPA completed the 60-week study as planned, which were not different (p = 0.678) (Fig. 2). Proportions of patients remaining at the end of TP were 86.5% in CBZ-CR (n = 90) and 79.6% in LTG + VPA (n = 78). SFR during the entire study period (60-week) was numerically higher in LTG + VPA (40.8%) than CBZ-CR (35.6%), but statistically not different (Risk Difference, 5.2%; 95% CI, −8.2%–18.6%, p = 0.444; p = 0.717; hazard ratio [HR], 0.92; 95% confidence interval [CI], 0.58–1.46; p = 0.717). However, SFR during the entire 52-week MP favored LTG + VPA than CBZ-CR, which were 64.1% and 47.8%, respectively (Risk Difference, 16.3%; 95% CI, 1.5%–31.2%, p = 0.034) (Fig. 2). TTFS during MP was also shorter in CBZ-CR than LTG + VPA (HR, 0.50; 95% CI, 0.27–0.93, p = 0.041) (Fig. 3). Although a significant minority of patients had history of prior AEDs use (10 patients in CBZ-CR and 13 patients in LTG + VPA), outcome analysis after their exclusion did not change the result (Table A.2 and Fig. A.2). Fifty-five patients of CBZ-CR and 56 patients of LTG + VPA completed the QoLIE-31 at the end of study, which were compared with their baseline scores. Although some improvements in all categories of QOL measure were found in each group, they were relatively small without any significant differences (Table 2).

3.4. Doses of study drugs

Mean doses of study drug at the end of study in patients who completed study were 650 ± 115 mg/day (500–1200 mg/day) in CBZ-CR and 82.2 ± 17.5 mg/day (53.6–168.8 mg/day) of LTG in LTG + VPA. Median doses of CBZ-CR and LTG were 600 mg/day and 75 mg/day, respectively. Sixty-four (67.8%) patients of CBZ-CR were kept on $\leq$ 600 mg/day during MP and 49 of 61 (80.3%) patients who achieved SF during MP were taking CBZ-CR $\leq$ 600 mg/day. Corresponding numbers of LTG + VPA were 52 (66.7%) patients and 46 (88.5%) of 52 patients, respectively. Therefore, doses at or less than ITD were sufficient to achieve seizure freedom in a majority of patients.

3.5. Tolerability

A similar proportion of patients in CBZ-CR and LTG + VPA experienced at least one AE during the treatment period, with most events being mild or moderate in intensity. Sixty of 104 (57.7%) patients of CBZ-CR reported 222 AEs, while 59 of 98 (60.2%) patients of LTG + VPA reported 227 AEs. Investigators indicated that 67 AEs reported by 29 (27.9%) patients in CBZ-CR and 52 AEs reported by 27 (27.6%) patients in LTG + VPA were study drug-

Table 1
Baseline demographics and clinical features of patients.

Variables		CBZ-CR (n = 104)	LTG + VPA (n = 98)	P-value
Age (years)	Mean (SD)	33.2 (14.6)	36.5 (13.7)	0.098
Sex	Male	53 (51.0%)	50 (51.0%)	0.993
Body weight (kg)	Mean (SD)	63.7 (9.8)	61.9 (11.7)	0.253
BMI (kg/cm^2)	Mean (SD)	23.3 (2.7)	22.6 (3.2)	0.115
History	Febrile convulsion	7 (6.7%)	8 (8.2%)	0.698
	Remote brain insults	7 (6.7%)	11 (11.2%)	0.326
	Family history of epilepsy	6 (5.8%)	3 (3.1%)	0.623
AEDs therapy	None	80 (76.9%)	73 (74.5%)	0.709
	Emergency only	14 (13.5%)	12 (12.2%)	
	Previously treated	10 (9.6%)	13 (13.3%)	
Neurologic exam	Mental retardation	3 (2.9%)	3 (3.1%)	0.450
	Focal neurologic signs	3 (2.9%)	2 (2.0%)	0.195
Total number of seizures	For 6 months: mean (SD)	8.8 (27.6)	8.6 (27.1)	0.972
	median (IQR)	2.0 (3.5)	2.0 (3.0)	
	For 3 months: mean (SD)	5.6 (13.8)	5.3 (13.7)	0.890
	median (IQR)	2.0 (3.0)	2.0 (2.0)	
Epilepsy syndromes	Localization–related	89 (85.6%)	78 (79.6%)	0.261
	– cryptogenic	54 (60.7%)	48 (61.5%)	
	– symptomatic	35 (39.3%)	30 (38.5%)	
	– lesion (+MRI)	30 (33.7%)	25 (32.5%)	
	Undetermined	15 (14.4%)	20 (20.4%)	

CBZ-CR, controlled release-carbamazepine; LTG + VPA, combination of lamotrigine and valproate; SD, standard deviation; IQR, interquartile range; BMI, body mass index; AEDs, antiepileptic drugs; (+MRI), number of patients with lesion in MRI; GTCS, generalized tonic-clonic seizures; Student's *t*-test, χ^2 test or Fisher's exact test if any frequency count was < 5.

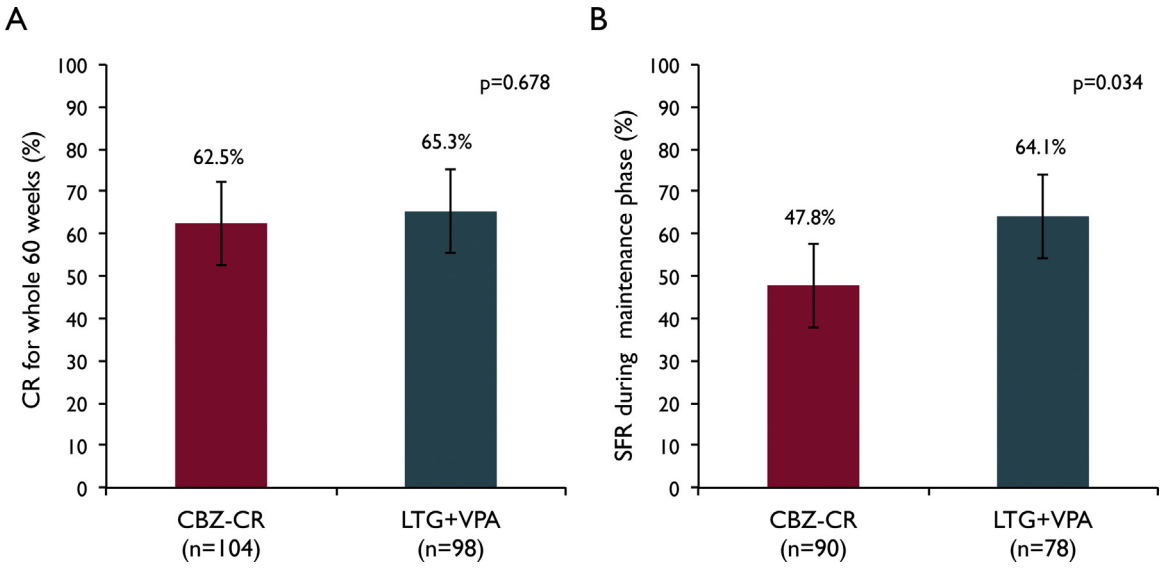

Fig. 2. Diagram of outcome measures.
A. Completion rates of patients assigned to CBZ-CR monotherapy and LTG and VPA combination therapy. B. Seizure free rates during maintenance phase.
CR, completion rate (a proportion of patients who finished the 60-weeks study planned);
SFR, seizure free rate; CBZ-CR, controlled-release carbamazepine; LTG + VPA, combination of lamotrigine and valproate.

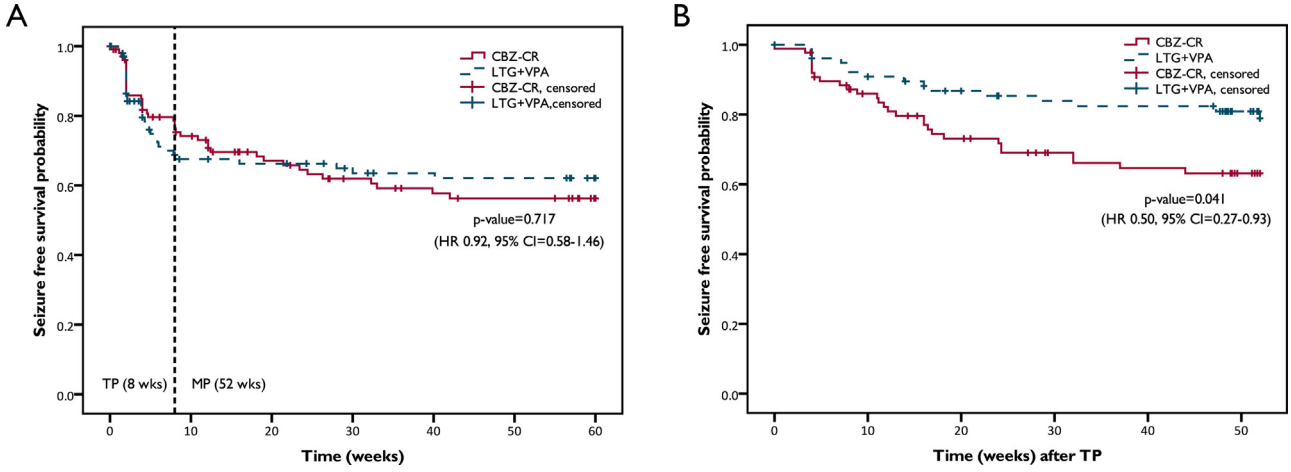

Fig. 3. Survival curve of time to first seizure.
A. Time to first seizure from the start of study showed that the patients assigned to CBZ-CR showed longer time to seizure during the titration phase, but became shorter throughout maintenance phase. Comparison of two groups throughout the whole study period did not show any significant difference (p = 0.717). B. Time to first seizure from the beginning of maintenance phase disclosed that patients assigned to LTG + VPA took longer time to first seizure than patients assigned to CBZ-CR throughout 52 weeks of maintenance phase, which was statistically significant (p = 0.041).
TP, titration phase; MP, maintenance phase; wks, weeks.

related. Treatment emergent adverse events (TEAEs) that were reported in ≥ 5% of patients were summarized in Table 3. Among TEAEs, tremor was more frequently reported in LTG + VPA (p = 0.016). Fatigue and ataxia were slightly more common in CBZ-CR and pruritus in LTG + VPA. Seven of CBZ-CR and six of LTG + VPA developed skin rash. None of patients developed Steven-Johnson syndrome (SJS) or toxic epidermal necrolysis during the study. Thirteen (12.4%) patients of CBZ-CR and seven (7.1%) of LTG + VPA were withdrawn from the study due to AEs (Table A.3). In CBZ-CR, skin rash was responsible for premature drug withdrawal in six patients, elevation of liver enzyme in two patients, and memory impairment, dyspepsia, anxiety with irritability, alopecia, and pruritus were reasons for study termination in five patients. In LTG + VPA, three patients were dropped-out due to skin rash and two patients each were withdrawn due to intolerable headache (one patient reported additional dyspepsia), and gastrointestinal discomfort. A total of 10 serious AEs (SAE) were reported in nine patients, all of whom were taking CBZ-CR, which were herpetic meningoencephalitis, pneumonia, GTCS, ventricular tachycardia, forearm fracture, joint dislocation, facet joint syndrome, abnormal behavior, and skin rash. Among those, only one patient with skin rash was considered study drug-related.

4. Discussion

CR, the primary outcome measure, was comparable between two groups. However, SFR for 52-week MP and TTFS starting from MP, secondary outcome measures, favored LTG + VPA. The survival curve of TTFS (Fig. 3) illustrated that seizure occurrences during TP was higher in LTG + VPA than CBZ-CR, which was reversed from the beginning of MP. Reasons for the opposite pattern of seizure occurrences related to treatment phases are unclear. We speculate

Table 2
Results of outcome measures.

Primary outcome	CBZ-CR (n = 104)	LTG + VPA (n = 98)	P-value
Completion rate for whole 60 weeks	65 (62.5%)	64 (65.3%)	0.678
Secondary outcome			
Seizure free for whole 60 weeks from the study	37 (35.6%)	40 (40.8%)	0.444
Among the patients with TP completion[α]	(n = 90)	(n = 78)	
1) Seizure Free for the first 24 weeks of MP	51 (56.7%)	59 (75.6%)	0.010
2) Seizure Free for the entire 52 weeks of MP	43 (47.8%)	50 (64.1%)	0.034
QoLIE-31			P-value
Overall QOL			
Baseline	59.18 ± 16.05	58.01 ± 17.67	0.668
End of study	63.80 ± 17.97	65.61 ± 18.83	0.604
Change (End of study– Baseline)	3.10 ± 20.93	5.89 ± 17.15	0.404
Overall score			
Baseline	64.63 ± 14.98	65.69 ± 15.90	0.685
End of study	70.50 ± 14.78	71.37 ± 15.89	0.777
Change (End of study–Baseline)	5.61 ± 15.01	4.20 ± 13.53	0.755

CBZ-CR, controlled release-carbamazepine; LTG + VPA, combination of lamotrigine and valproate; TP, titration phase; MP, maintenance phase; QOL, quality of life. QoLIE-31, Quality of Life in Epilepsy Inventory-31; [α]Number of patients with TP completion: n = 90 (CBZ-CR) and n = 78 (LTG + VPA); c^2 test for primary outcome, Cox proportional hazards model for secondary outcome, and mixed model analysis for QoLIE-31.

Table 3
Treatment emergent adverse events reported in ≥ 5% of study patients.

Adverse events	CBZ-CR (n = 104)	LTG + VPA (n = 98)	P-value
Headache	26 (25.0%)	26 (26.5%)	0.930
Dizziness	18 (17.3%)	17 (17.3%)	1.000
Somnolence	14 (13.5%)	12 (12.2%)	0.962
Memory impairment	10 (9.6%)	5 (5.1%)	0.340
Fatigue	10 (9.6%)	4 (4.1%)	0.204
Tremor	2 (1.9%)	11 (11.2%)	0.016
Ataxia	6 (5.8%)	1 (1.0%)	0.145
Skin rash	7 (6.7%)	6 (6.1%)	1.000
Pruritis	2 (1.9%)	7 (7.1%)	0.145
Dyspepsia	7 (6.7%)	5 (5.1%)	0.848
Weight gain	9 (8.7%)	6 (6.1%)	0.676
Weight loss	5 (4.8%)	5 (5.1%)	1.000
Nasopharyngitis	7 (6.7%)	10 (10.2%)	0.525
Depression	5 (4.8%)	5 (5.1%)	1.000
Arthralgia	4 (3.8%)	6 (6.1%)	0.674

that the adoption of a slow dose- titration schedule and lower target dose of LTG than the prescription information (increase of LTG to 75 mg/day instead of 100 mg/day at 5th week) might have resulted in low serum concentrations of LTG during the later half of TP and was responsible for higher seizure occurrences. Once VPA was added to LTG at 7th week, the steady state of LTG + VPA concentration was reached at the end of TP (5 times of half-life of LTG is about 12.5 days), thus become more effective from the beginning of MP. On the other hand, the titration phase of this trial might have been longer than usual for titration of CBZ-CR, which might have penalized CBZ-CR arm. Although future investigations employing blood-level measurement are required for better explanation of higher seizure occurrences during TP in LTG + VPA, if we consider that the starting point for assessing efficacy should exclude any pharmacokinetic differences between CBZ-CR and LTG + VPA, seizure outcomes during MP, after stabilization of pharmacokinetic interactions, would be clinically more meaningful. However, it is also possible that seizure freedom during MP might have been affected by the inadequate maintenance dose of CBZ-CR that could have been reached only after repeated attempts. Therefore, future longer-term pragmatic trials comparing CBZ-CR and LTG + VPA in adequate maintenance doses are needed.

Both regimens were quite comparable in safety and tolerability measures. Incidences of TEAEs were comparable and the premature withdrawal rate due to AEs was numerically higher in CBZ-CR, but statistically not different. Skin rash was a major concern for the safety of LTG + VPA [24], however, it was turned out not a problem. Study drugs were prematurely withdrawn due to skin rash in only three (3.1%) patients of LTG + VPA compared to six of CBZ-CR, and none had developed severe skin reactions like SJS. Previous investigators have found that the adoption of slow dose-titration is important to decrease the risk of skin rash [25] and add-on of VPA to patients already taking LTG didn't increase the risk of skin rash [16], which was in good agreement with our results. Positional tremor was the only AE more frequent in LTG + VPA, which was reported in 11 patients compared to only two in CBZ-CR. In previous studies of LTG + VPA [16,17], tremor was found very frequently (≥50% of patients) and sometimes quite disabling [26]. Emergence of tremor seems to be, at least partly, dose-related, which may improve after dose reduction of either VPA or LTG. Use of much lower doses of LTG and VPA than other studies [16–18] might explain the lower incidence of tremor, which was mild in all patients.

We chose LTG + VPA as the comparator of CBZ-CR monotherapy for initial drug-regimen in patients with untreated epilepsies. All three AEDs are first-line drugs for PS and GTCS [6]. Although there is a concern for using CBZ in patients with idiopathic generalized epilepsies, we did exclude those patients by using semiology-EEG-MRI correlations based on ILAE-classification system [22]. Among 35 patients classified into undetermined epilepsy (UE), six patients showed generalized interictal epileptiform discharges in EEG but had clear focal features in semiology and any patients with previous episodes of absence seizures or myoclonic seizures were excluded from the study. Therefore, we felt that baseline demographic features were equally balanced between two groups. Combination of LTG and VPA was first reported to carry synergistic interactions by Brodie et al. [11], who had shown a higher responder rate of LTG add-on in patients taking VPA monotherapy. Pisani et al. [15] reported a significant improvement of seizure control by their combination in patients who failed to the monotherapy of VPA and LTG. Subsequently, extensive clinical experiences have been accumulated to propose it as the most effective combination regimen in patients suffering from DRE [17–19]. Therefore, LTG + VPA is considered a good candidate for the trial aiming at better outcome than monotherapy as initial drug-regimen in patients with untreated epilepsy.

CBZ-CR 600 mg/day is the standard dose in monotherapy, however, there is no information about the optimal doses of LTG + VPA as initial drug regimen. ITD of LTG in monotherapy is 150 mg/day to 200 mg/day and VPA varies from 600 mg/day to 1000 mg/day. LTG + VPA carries significant pharmacokinetic

interactions, primarily resulting from the inhibition of UGT1A4 by VPA, the key metabolizing enzyme. LTG clearance decreases more than 50% by VPA to prolong the half-life of LTG from 24 to about 60 h [27]. Therefore, dosage of LTG should be reduced by a half when VPA is added to the regimen, which was the reason for the adoption of LTG 75 mg/day as ITD. The effective dose of VPA for the maximal inhibition of LTG metabolism is low. Gidal et al. [28] showed that the clearance of LTG was significantly reduced by VPA 250 mg/day and reached to the maximal inhibition at ≤ 500 mg/day. Therefore, VPA 500 mg/day was considered adequate for the maximum benefit of pharmacokinetic interaction although its optimal dosage for synergistic pharmacodynamic interactions is unknown.

For this study, we were interested in comparing the two drug regimens at equivalent TDL. The concept of TDL, total daily dose divided by WHO-recommended daily dose, is an attractive hypothesis in explaining the emergence of AEs in combination therapy [29]. The TDL of CBZ 600 mg/day is 0.6 and TDL of LTG 75 mg/day + VPA 500 mg/day is 0.58 (WHO-recommended daily dose of LTG and VPA are 300 mg/day and 1500 mg/day, respectively), thus they are quite comparable. The result of study also seems to support the adequacy of ITD of CBZ and LTG + VPA because more than 80% of patients who had achieved SF during MP did so at their ITD. Apparently, ITD of LTG + VPA in this study was much lower than mean prescription doses of same regimen in patients with DRE, which were LTG 155 mg/day and VPA 1200 mg/day, respectively [30]. Despite using low dose LTG + VPA, SFR during MP was higher in LTG + VPA than CBZ-CR, which was considered another evidence indicating their synergistic interactions.

Important advantage of LTG + VPA is once a day dosing due to prolonged LTG half-life. Although there may be some controversy about once a day dosing of VPA, it has been shown that once daily administration of enteric-coated sodium valproate is as effective as twice daily dosing [31]. Therefore, LTG + VPA once a day dosing is appropriate to provide practical advantages of more convenience and better compliance. Although the compliance rates in this study were high in both regimens, once a day dosing is associated with better compliance in patients requiring chronic treatment [32]. Recently, sustained release forms of new AEDs including extended release form of LTG (LTG-XR) [33] became available for once a day dosing. However, most of them are not available yet in many countries (including Korea). Prices of new AEDs including LTG are still too high to be easily affordable in many part of the world. In this regard, LTG + VPA may provide an advantage of cost reduction by decreasing the dose of LTG to half, thus contribute to its easier affordability as initial drug regimen. Other advantages may include lack of potential risks of hepatic enzyme-inducing drugs, a major concern in patients taking concomitant medications for comorbidities. For those patients, adoption of low dose LTG + VPA in once a day dosing may provide an alternative solution. Both LTG and VPA are prototype broad-spectrum AEDs, which may have more advantages for their combination as initial drug regimen in patients with uncertain diagnosis of seizure types or multiple types of seizures.

In this study, women planning to be pregnant or not using appropriate contraceptive measures were excluded and none of patients became pregnant during the study period. However, since the implementation of our study in July 2008, there have been growing concerns for the use of LTG + VPA in women of reproductive age due to increasing evidence of in-utero exposure of VPA for higher teratogenicity and neurobehavioral AEs [34,35], Practice parameters published in 2009 [36] recognized the high risk of VPA as Level B evidence and recommended to, if possible, avoid VPA and AED polytherapy during the first trimester of pregnancy to decrease the risk of major malformations and cognitive outcomes. At the end of 2014, European Medicines Agency (EMA website) published a report advising not to use VPA in women of reproductive age, which was further revised by ILAE and European Academy of Neurology in 2015 [37]. Although low dose of VPA (≤700 mg/day) carries significantly less risks of fetal complications than its higher dose and its combination with other drugs may not increase the risk further [38], LTG + VPA should be avoided in women of reproductive age to comply with the current recommendation [37].

Our study has several limitations. Unblinded study design is liable to both type 1 and type 2 errors, although patients were randomized appropriately and the study progression and data analysis were conducted according to the GCP guidelines. Future RCTs are needed to provide class 1 evidence promoting LTG + VPA as the initial drug regimen. The number of patients recruited to the study was slightly less than that initially planned, however, number of cases subjected to data analysis was higher than the pre-trial estimation (104 in CBZ-CR and 98 in LTG + VPA compared to 94 patients each), thus it is unlikely to affect the outcome of study. Although blood-level measurement may help detect noncompliance and avoid outliers showing abnormally high or low blood levels, especially in patients of LTG + VPA carrying significant pharmacokinetic interactions, blood level measurements of new AEDs were not available in many participating centers. Lastly, it is unclear whether the low-dose combination of LTG + VPA is going to improve the long-term outcome of AEDs therapy, which is at the stage of hypothesis at present. Future long-term randomized clinical trials are clearly needed.

In conclusion, the study failed to show that LTG + VPA is superior to CBZ-CR as initial drug regimen in patients with untreated PS and/or GTCS. However, SFR and TTFS during MP were in favor of LTG + VPA to suggest low dose LTG + VPA as an option for initial drug regimen in patients requiring once a day dosing, prescription of non-enzyme inducing AEDs, or broad-spectrum AEDs, but not in women of reproductive age. Comparative RCTs of CBZ-CR and LTG + VPA in newly diagnosed patients with epilepsy are in urgent need.

Conflicts of interests

BI Lee has received honorarium from UCB and Esai and has done consulting for Esai. None of co-authors have any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2017.12.008.

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