Heliyon 9 (2023) e17384

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Efficacy and safety of zonisamide as the first additional treatment in Chinese patients with focal or secondary bilateral tonic–clonic seizures: An observational ,prospective study

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ARTICLE INFO

Keywords:
Zonisamide
Epilepsy
Anti seizure medicine
Focal-onset seizures
Secondary bilateral tonic–clonic seizure
sBTCS

ABSTRACT

Background: To evaluate the efficacy and safety of zonisamide (ZNS) as the first additional treatment for focal or secondarily bilateral tonic–clonic seizure (sBTCS).
Methods: A total of 118 patients between 18 and 75 years of age with focal or sBTCS were recruited from multiple hospitals in Shandong province between May 13, 2021, and February 16, 2022. All received ZNS as the first additional treatment after clinical judgment. Seizure frequency, retention, and adverse events (AEs) were assessed 2 and 5 months after the introduction of ZNS.
Results: Overall response rates at 2 and 5 months were 79.5% and 75.5%, respectively, whereas seizure-free rates at the same point were 53.6% and 51%, respectively. The review's retention rates at 2 and 5 months were 95% and 86%, respectively. The most common AEs were anorexia with weight loss (11.8%), dizziness (6.9%), and headache (3.9%).
Conclusions: Our real-world study confirmed the efficacy and safety of ZNS as a first-additional treatment for focal or sBTCS in Chinese patients, with a high short-term retention rate.

1. Introduction

Epilepsy is a common neurological disease caused by the highly synchronized abnormal discharge of neurons in the brain, and its clinical onset is episodic, transient, stereotypic, and repetitive [1]. More than 70 million people worldwide are affected by epilepsy [2]. It is estimated that there are about 10 million epilepsy patients in china of which only about one third has received appropriate or adequate treatment [3]. This inadequate treatment results in decline in patient's quality of life, education and employment prospects [4]. Anti Seizure Medicines (ASMs) are the primary means to treat epilepsy; however, approximately 30% of patients do not achieve seizure control using single anti seizure medicine [5]. Therefore, clinical research is necessary for discovering new combination therapies for patients with epilepsy. ZNS is a second-generation anti Seizure Medicine that has been shown to have multiple

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https://doi.org/10.1016/j.heliyon.2023.e17384
Received 14 October 2022; Received in revised form 11 June 2023; Accepted 15 June 2023
Available online 20 June 2023

mechanisms of action [6]. First, it is related to blocking voltage-dependent sodium channels and T-type calcium channels. [7]; second, it enhances γ-aminobutyrate (GABA) mediated inhibition by increasing the release of presynaptic GABA and inhibiting its reuptake in the synaptic cleft [8]; and finally, it reduces glutamate-induced excitation and is a weak inhibitor of carbonic anhydrase [9]. Although the clinical relevance of these mechanisms to antiepileptic activity is still unclear [10], These multiple mechanisms of action make zonisamide effective in both focal and generalized seizures, making it add-on treatment of choice for most seizure types [11]. ZNS originated in Japan and was produced by the Sumitomo Pharmaceutical R&D in-review laboratory. Early clinical studies have confirmed that it has a long half-life and good tolerance. Phase II and III trials have proven the drug efficacy and safety for focal or sBTCS; in 1989, ZNS was approved for marketing in Japan. Studies after the marketing, and more than 10 years of clinical observation data, supported its effectiveness as monotherapy for various seizure types and epileptic syndromes [12]. Thereafter, it was approved for use in Korea in 1992, the United States in 2000, and Europe in 2005. The drug was approved in Korea and the United States for the additional treatment of adults with focal seizures (with or without secondary generalized seizures). In Europe, it was also used as monotherapy for the treatment of newly diagnosed focal or generalized seizures in adults [13].

In 2009, the drug was approved as an additional treatment for focal seizures in adults in China. Although ZNS has been in the market in China for more than a decade, there are few real-world studies on it as a first additional treatment for focal seizures or sBTCS. Therefore, we conducted a prospective real-world study to provide clinical data on ZNS as the first additional therapy for focal or sBTCS in patients with epilepsy and evaluate its efficacy and safety.

2. Methods

2.1. Selection of respondents

Patients with focal or sBTCS who were admitted to Qilu Hospital of Shandong University; Shandong Provincial Hospital of Shandong University; Qianfoshan Hospital of Shandong University; and Changguo Hospital of Zibo City, Shandong Province between May 13, 2021, and February 16, 2022, were enrolled. Informed consent was obtained and signed by all patients. This study was conducted in accordance with the Declaration of Helsinki and approved by the medical ethics committee of Qilu Hospital of Shandong University (NO. Kyll-2021034). The test has been approved and available on: http://www.chictr.org/cn/ registered (ChiCTR2100047311, June 12, 2021). Inclusion criteria were: (a) consent to participate in the clinical trial and signed informed consent from the patient or legal guardian, (b) men and women aged 18–75 years, (c) meeting the International League Against Epilepsy (ILAE) 2017 diagnostic criteria for focal epilepsy or sBTCS, (d) patients who had adherently taken one anti seizure medicine during the previous 4 weeks and were considered by the investigator to be appropriate for ZNS addition, and (e) at least two or more focal episodes every 28 days during the 8-week retrospective baseline period.

In contrast, the exclusion criteria were: (a) previous treatment with ZNS; (b) pregnant and lactating women, and those who refused contraception usage during the trial; (c) history of allergies to sulfanilamide or ZNS or any of its excipients; (d) history of drug/alcohol abuse; (e) history of attempted suicide or suicidal ideation in the past 6 months; (f) current use of Antidepressants, anxiolytics, or antipsychotics; (g) Progressive diseases that affect the patient's brain and its function; (h) psychogenic non-epileptic seizures; (i) presence of severe lung and blood system diseases, malignant tumors, immune dysfunction, and mental health conditions; (j) patients who have undergone epileptic brain surgery or are scheduled to undergo epileptic brain surgery within the next 4 months; and (k) patients deemed ineligible for the trial by the investigator.

2.2. Study design

A 5-month prospective multicenter study was performed to evaluate the efficacy and safety of ZNS. The following clinical data of the patients were collected: sex, age, height, weight, BMI, education level, age of epilepsy onset, duration of epilepsy, etiology, seizure type (focal or sBTCS), adherence to ASMs in the past 4 weeks, seizure frequency in the past 8 weeks, and anxiety, depression, and cognitive function Mini-Mental State Examination Scale (MMSE) results. A case report form (CRF) was used to collect and record the clinical data of patients. All enrolled patients received an initial dose of 100 mg/day, which was titrated by 100 mg every 2 weeks according to clinical response and tolerability to the optimal dose, with a maximum dose of 400 mg/day. The concomitant anti seizure medicine dose and type were constant.

2.3. Outcome evaluation

Efficacy was assessed by measuring changes from the baseline seizure frequency at 2 and 5 months of follow-up. The baseline was 2 months before the addition of ZNS, and seizure frequency was based on CRF records during follow-up. For the efficacy evaluation, we classified patients into five categories: (1) no seizures, (2) reduction in seizure frequency of $\geq$50%, (3) reduction in seizure frequency of $<$50%, (4) no change, and (5) worsening (patients with increased seizures). Responders were defined as patients with a reduction in seizure frequency of more than 50% or no seizures at the final follow-up time (patients with sBTCS were defined as having a reduction in all seizure types). At each follow-up, tolerability and safety were assessed by reported AEs, discontinuation of ZNS, and clinical laboratory tests (hematology, clinical chemistry, and urinalysis). AEs were primarily based on direct patient reports.

2.4. Statistical analysis

All analyses were performed using the statistical package R 3.3.2 (HTTP://www.R-project.org, the R Foundation) and Free Statistics software version 1.7. Descriptive analysis was used, and categorical variables were expressed as proportions (%). As appropriate, continuous data are expressed as mean and standard deviation (SD). For inter-group comparisons, Student's t-test was used to compare continuous variables subject to normal distribution, whereas the non-parametric Mann-Whitney *U* test was used to compare continuous variables that were non-normally distributed. Categorical variables were compared using the chi-squared or Fisher's exact tests. Kaplan–Meier survival curves assessed the retention of ZNS. Cox regression analyses were used for the multifactor analysis of treatment effects, and the odds ratio (HR) and 95% confidence interval (CI) were calculated. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Study population

For this study, total number of patients were 118, based on the 2017 ILAE diagnostic criteria, that used ZNS as the first additional treatment for epilepsy were reviewed. Five individuals were lost to follow-up, four discontinued the drug due to its perceived ineffectiveness, two withdrew from the study because they were unwilling to continue participating, two withdrew due to headache, two withdrew for fear of adverse reactions and drug withdrawal, and one discontinued the drug due to loss of appetite. Finally, 102 patients (57 men and 45 women) were enrolled in our study. The inclusion criteria are shown in Fig. 1.

Of the 118 patients ，he mean age of the enrolled patients was 35.6 ± 15.1 years (range, 18–75 years), onset age of epilepsy was

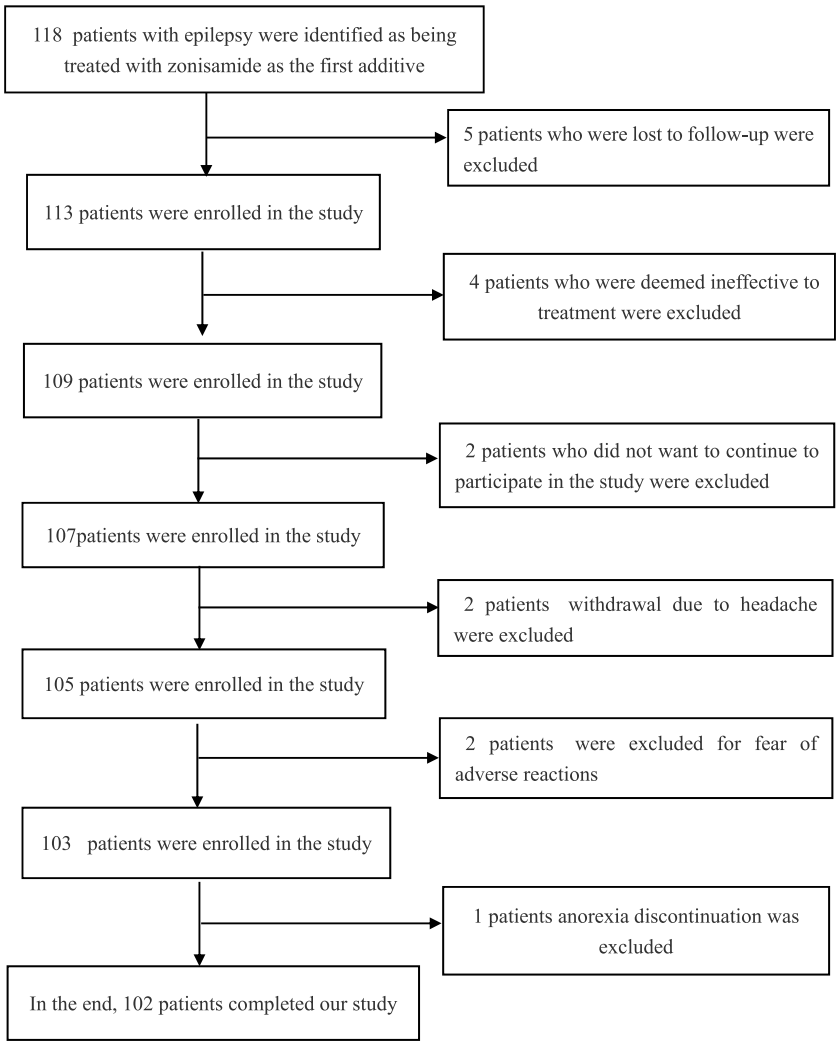

Fig. 1. Flow chart.

28.0 ± 16.4 years, and duration of epilepsy was 8.1 ± 8.8 years. The epilepsy etiologies included structural (n = 71; 60.2%), infectious (n = 14; 11.9%), metabolic (n = 4; 3.4%), genetic (n = 2; 1.7%), immune (n = 2; 1.7%), and unknown (n = 25; 21.2%). Regarding the types of epilepsy, focal seizure was recorded in 36 patients (30.5%), whereas 82 patients (69.5%) was recorded with focal to bilateral tonic–clonic seizure. The number of seizures in the previous 8 weeks was 8.6 ± 15.6. Concomitant ASM was also divided into enzyme-inducing antiseizure medication (EIASM) (52 cases, 44.1%) and non-EIASM (66 cases, 55.9%). 34 patients (12.5 ± 8.0) had mild to severe depression, according to the Hamilton Depression-17 scale (HAMD-17) and 38 patients (14.1 ± 7.3) had anxiety, ranging from possible anxiety to severe anxiety, according to the Hamilton Anxiety Scale (HAMA). 30 patients (22.3 ± 5.1) had mild to moderate cognitive impairment, scored using the MMSE scale. All patients had taken only one anti seizure medicine in the previous 4 weeks. Baseline demographic and clinical characteristics of the patients are shown in Table 1.

3.2. Retention rate

The 2-month retention rate was 95% (112/118). Six patients discontinued treatment, including one who stopped the treatment due to poor response; two did not want to continue participating in the study, and two who stopped because of headache, and one who was not able to follow-up (Fig. 2).

The retention rate at 5 months was 86% (102/118). Ten patients stopped treatment, four were unable to do a follow-up, three thought the treatment was ineffective, two stopped the treatment because of fear of adverse reactions, and one in-review patient stopped treatment because of appetite loss. The overall retention rate is shown in Fig. 2.

3.3. Efficacy

At the 2-month follow-up, 112 patients participated in the efficacy evaluation. The overall response rate (seizure reduction ≥50%) at 2 months was 79.5% (89/112); 53.6% (60/112) of patients achieved a seizure-free state, 25.9% (29/112) had a reduction of ≥50%, and 12.5% (14/112) had seizure frequency <50%, 8% (9/112) patients with no change or worsening in seizure frequency (Fig. 3).

At the 5-month follow-up, the 102 patients also participated in an efficacy evaluation. The overall response (seizure reduction ≥50%) at 5 months was 75.5% (77/102); 51% (52/102) had no seizure, 24.5% (25/102) had seizure frequency reduction ≥50%, 7.8% (8/102) had seizure frequency reduction <50%, and 16.8% (17/102) had no change or deterioration in seizure frequency (see Fig. 3).

After the 5-month follow-up, the final efficacy assessment was divided into treatment responders (≥50% improvement in seizures) and non-responders (<50%). There were no significant differences in sex, height, weight, BMI, education level, enzymes, and non-

Table 1
Demographical and clinical characteristics of patients.

Variables	Total (n = 118)
Sex, n (%)	
Female	54 (45.8)
Male	64 (52.4)
Age, years Mean ± SD	35.6 ± 15.1
Height, meter Mean ± SD	1.7 ± 0.1
Weight, kg Mean ± SD	67.0 ± 13.3
BMI, Mean ± SD	19.9 ± 3.6
Degree of education, n (%)	
Less than 12 years	69 (58.5)
More than 12 years	49 (41.5)
Age at epilepsy onset, Mean ± SD	28.0 ± 16.4
Epilepsy duration, Mean ± SD	8.1 ± 8.8
Etiology, n (%)	
Structural	71 (60.2)
Infection	14 (11.9)
Metabolic	4 (3.4)
Genetic	2 (1.7)
Immune	2 (1.7)
Unknown	25 (21.2)
Seizure type, n (%)	
Secondarily bilateral tonic–clonic seizure	82 (69.5)
Focal	36 (30.5)
Seizure frequency in previous 8 weeks, Mean ± SD	8.6 ± 15.6
Concomitant ASMs, n (%)	
EIASMs	52 (44.1)
Non-EIASMs	66 (55.9)
HADM.17, Mean ± SD	34 (12.5 ± 8.0)
HAMA, Mean ± SD	38 (14.1 ± 7.3)
MMSE, Mean ± SD	30 (22.3 ± 5.1)

ASMs: Anti Seizure Medicines; EIASMs:enzyme inducer ASMs; HAMD-17: Hamilton Depression-17 scale; HAMA:Hamilton Anxiety Scale; MMSE: Cognitive Function Mini-Mental State Examination Scale.

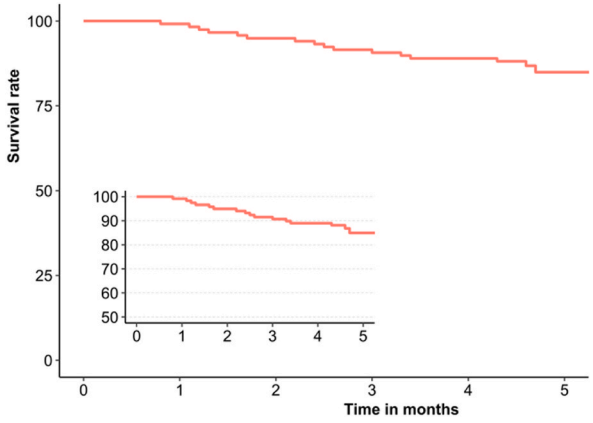

Fig. 2. Estimated retention rate in the patients treated with for the first time adjunctive zonisamide using Kaplan-Meier survival analysis.

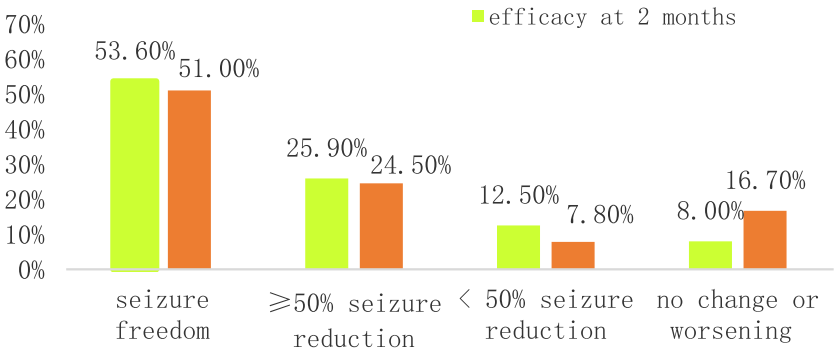

Fig. 3. Efficacy of ZNS at 2 and 5 months follow-up.

enzymes between responders and non-responders. Notably, we found that the responder's age and age at epilepsy onset was greater than that of the non-responders (35.7 ± 16.4 vs. 31.4 ± 10.0, $P = 0.229$ and 29.2 ± 17.9 vs. 22.9 ± 12.1, $P = 0.106$, respectively). The duration of epilepsy in non-responders was longer than in responders ($P = 0.193$). Regarding etiology, structural (44/77, 57.1%), infectious (10/77, 13%), and unknown (18/77, 23.4%) had better efficacy, although not statistically significant. Finally, patients with focal and sBTCS had better outcomes.

Moreover, there was no significant difference the Seizure frequency in previous 8 weeks. Valproate, oxcarbazepine, levetiracetam, and carbamazepine are commonly used antiseizure drugs. Most patients only require 200–300 mg/day to have a good effect. After 5 months of treatment with ZNS 200–400 mg/day, there was no significant difference in the HADM.17 and HAMA scores between the two groups. Patients with anxiety, depression, and cognitive dysfunction showed limited improvement, and the number of patients with depression decreased from 34, before treatment, to 13. HAMD-17 (12.5 ± 8.0 vs. 7.4 ± 5.1); the number of people with anxiety dropped from 38 before treatment to as few as 23, HAMA (14.1 ± 7.3 vs. 8.5 ± 5.7). The number of patients with cognitive impairment decreased from 30 before treatment, to 14, and the MMSE was (22.3 ± 5.1 vs. 24.9 ± 3.9). We found that the MMSE score of those responsive to treatment was higher than for those who did not respond to treatment (25.7 ± 3.4 vs. 22.8 ± 4.6, $P = 0.043$). This suggests that ZNS may improve cognitive impairment in patients who respond to treatment (See Table 2 for more data comparisons).

Cox multifactorial regression was used to analyze the effects of variables with P values < 0.1 (seizure frequency at 8 weeks, and MMSE score; Table 2); the variables that we considered to be meaningful in this study, based on clinical experience (age, age at epilepsy onset, and epilepsy duration); and daily ZNS dose on the treatment effect. We found that 8 of seizure frequency influenced the final treatment response; however, this is well known. MMSE, age, age at epilepsy onset, epilepsy duration, and daily ZNS dose did not show independent effects (Table 3).

3.4. Safety

Twenty-two of 102 patients (21.6%) experienced at least one AE during the ZNS treatment (5-month follow-up), with a total of 33 AEs reported (two additional patients discontinued treatment due to headache intolerance, and one due to anorexia, for whom data were not included). The mean dose of ZNS did not differ significantly between patients who experienced AEs and those who did not (200–400 mg, $P = 0.234$). Anorexia with weight loss was the most common AE (11.8%, 12/102). Eight patients had anorexia with weight loss, and four had anorexia without weight loss, followed by dizziness (6.9%, 7/102), headache (3.9% , 4/102), and

Table 2
Comparison of demographics and related variables between responders and non-responders.

Variables	Total (n = 102)	Responders (n = 77)	Non-responders (n = 25)	*P* value
Sex, n (%)				0.347
Female	45 (44.1)	36 (46.8)	9 (36)	
Male	57 (55.9)	41 (53.2)	16 (64)	
Age, years Mean ± SD	34.6 ± 15.2	35.7 ± 16.4	31.4 ± 10.0	0.229
Height, meter Mean ± SD	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	0.101
Weight, kg Mean ± SD	67.3 ± 14.0	66.4 ± 13.4	69.8 ± 15.7	0.297
BMI, Mean ± SD	20.0 ± 3.7	19.8 ± 3.5	20.5 ± 4.3	0.441
Degree of education, n (%)				0.347
Less than 12 years	57 (55.9)	41 (53.2)	16 (64)	
More than 12 years	45 (44.1)	36 (46.8)	9 (36)	
Age at epilepsy onset, Mean ± SD	27.6 ± 16.9	29.2 ± 17.9	22.9 ± 12.1	0.106
Epilepsy duration, Mean ± SD	7.6 ± 8.1	7.0 ± 8.1	9.4 ± 7.7	0.193
Etiology, n (%)				0.612
Structural	58 (56.9)	44 (57.1)	14 (56)	
Infection	13 (12.7)	10 (13)	3 (12)	
Metabolic	3 (2.9)	1 (1.3)	2 (8)	
Genetic	2 (2.0)	2 (2.6)	0 (0)	
Immune	2 (2.0)	2 (2.6)	0 (0)	
Unknown	24 (23.5)	18 (23.4)	6 (24)	
Seizure type, n (%)				0.181
Secondarily bilateral tonic–clonic seizure	72 (70.6)	57 (74)	15 (60)	
Focal	30 (29.4)	20 (26)	10 (40)	
Seizure frequency in previous 8 weeks, Mean ± SD	8.9 ± 16.5	9.7 ± 18.6	6.6 ± 6.6	0.422
ConcomitantASMs, n (%)				0.555
VPA	29 (28.4)	20 (26)	9 (36)	
0XC	27 (26.5)	20 (26)	7 (28)	
LEV	17 (16.7)	14 (18.2)	3 (12)	
CBZ	16 (15.7)	14 (18.2)	2 (8)	
LAC	4 (3.9)	3 (3.9)	1 (4)	
PER	4 (3.9)	3 (3.9)	1 (4)	
LTG	3 (2.9)	1 (1.3)	2 (8)	
PHT	2 (2.0)	2 (2.6)	0 (0)	
Concomitant ASMs, n (%)				0.245
EIASM, n (%)	47 (46.1)	38 (49.4)	9 (36)	
Non-ASM, n (%)	55 (53.9)	39 (50.6)	16 (64)	
Seizure frequency at 8 weeks, Mean ± SD	2.7 ± 8.9	1.1 ± 3.6	7.7 ± 16.2	0.001
Seizure frequency at 20 weeks, Mean ± SD	3.6 ± 10.4	1.1 ± 2.9	11.3 ± 18.6	<0.001
Zonisamide.maintenance dose, n (%)				0.231
200	64 (62.7)	51 (66.2)	13 (52)	
300	29 (28.4)	21 (27.3)	8 (32)	
400	9 (8.8)	5 (6.5)	4 (16)	
HADM17, n, Mean ± SD	13 (7.4 ± 5.1)	10 (7.3 ± 5.5)	3 (7.6 ± 4.1)	0.895
HAMA, n, Mean ± SD	23 (8.5 ± 5.7)	19 (9.0 ± 6.1)	4 (7.0 ± 4.2)	0.352
MMSE, n, Mean ± SD	14 (24.9 ± 3.9)	9 (25.7 ± 3.4)	5 (22.8 ± 4.6)	0.043

ASMs: Anti Seizure Medicines; VPA,Valproicacid; LEV,levetiracetam; OXC,oxcarbamazeine; CBZ,carbamazepine.
LAC, lacosamide; PER, perampanel; LTG,lamotrigine; TPH: phenytoin.
ASMs, Anti-seizure medications; EIASMs, enzyme inducer ASMs; HAMD-17: Hamilton Depression-17 scale; HAMA:Hamilton Anxiety Scale; MMSE: Cognitive Function Mini-Mental State Examination Scale.

Table 3
Multivariate cox regression analysis for predictor of treatment response.

Variable	HR (95CI)	*P* value
Zonisamide.maintenance dose		
200 mg/day	1 (reference)	
300 mg/day	0.97 (0.38–2.51)	0.956
400 mg/day	1.51 (0.36–6.43)	0.575
Age	1.03 (0.92–1.16)	0.58
Age at epilepsy onset	0.94 (0.84–1.05)	0.249
Epilepsy duration	0.94 (0.84–1.05)	0.288
Seizure frequency at 8 weeks	0.92 (0.85–0.99)	0.023
MMSE	0.9 (0.78–1.04)	0.141

MMSE: Cognitive Function Mini-Mental State Examination Scale.

somnolence (3.9%, 4/102). The frequency of nausea (2.9%, 3/102), agitation (2%, 2/102), and mild rash (1%, 1/102) was low. Overall, AEs were mild and could be tolerated by most patients. One patient (2.2%) withdrew from ZNS treatment because of headache (some patients had more than one AE). The remaining patients completed the study due to tolerable AEs (Fig. 4).

4. Discussion

Our study evaluated the efficacy and safety of ZNS as the first additional treatment for focal or sBTCS. In this study, the 2-month retention rate was 95%, and the 5-month retention rate was 86%. Similar findings were also observed using ZNS as an additional therapy resulting in 3- and 6-month retention rates of 91.4% and 82.8%, respectively [14]. The differences observed may have been due to the shorter study period of the present study. However, the present study and previous studies have shown that ZNS has a high retention rate, which may be related to its good efficacy and tolerability.

A response rate of 79.5% and 75.5% after 2 and 5 months of ZNS administration, respectively, and a seizure-free rate of 53.6% and 51%, respectively were observed. Our findings of overall response and seizure-free rates are consistent with those of other studies [14, 15]. The marginally higher seizure-free rate may have been due to differences in patient groups between studies (e.g., ethnic groups, seizure duration, seizure type, and prior treatment). Notably, we found that the age of responders was higher than that of non-responders (35.7 ± 16.4 vs. 31.4 ± 10.0, $P = 0.229$), and age at epilepsy onset was marginally higher than that of non-responders (29.2 ± 17.9 vs. 22.9 ± 12.1, $P = 0.106$). This finding is consistent with those that showed good efficacy of ZNS in elderly patients [14, 16], suggesting that ZNS may be a better option for elderly patients with epilepsy. In addition, we found that structural (58/102, 56.9%), infectious (13/102,12.7%), and unknown (24/102, 23.5%) etiologies had better efficacy, although not statistically significant. The structural cause was consistent with studies conducted by Doğan et al. [17]. The results also show that ZNS was the best for seizure control in patients with epilepsy after stroke. In the present study, stroke patients accounted for a large proportion of cases of structural causes and showed a better treatment response, which corresponded to the previous finding that ZNS had a better effect on patients with older age and late age of onset for epilepsy. Additionally, ZNS was effective for patients with infectious and unknown etiologies. No studies support this finding, and randomized, double-blind studies with etiological classification are needed to validate our findings. Notably, in patients with focal epilepsy or secondary systemic tonic-clonic seizures, the treatment response after 8 weeks of ZNS (200–400 mg/ day) was a good predictor for the treatment response in the subsequent 20 weeks. This finding was consistent with the findings of Brigo et al. [18], wherein 8 weeks represented the shortest period over which changes in seizure frequency could be determined. Similarly, our study found that ZNS had a good effect on focal and sBTCS. In addition, current studies have found that ZNS was efficacious in patients with anxiety, depression, and cognitive impairment. As enzyme inducers may interfere with ZNS metabolism and reduce serum drug concentration, the plasma half-life of ZNS is reduced in the presence of enzyme inducers such as phenytoin, carbamazepine, or phenobarbital [19]; therefore higher doses may be required. However, the enzymatic inducer group in the present study did not require higher doses. Some studies have shown that although ZNS has effects on liver metabolism, its pharmacokinetic interaction potential is low, and there are no effects on the plasma concentrations of carbamazepine [20], valproate [21], and lamotrigine [22]. However, a marginal reduction or elimination of phenytoin [23] was observed.

Additionally, some studies have shown that ZNS had a significant effect on CBZ metabolism, and the concentration of carbamazepine epoxide, a metabolite of carbamazepine, may increase with increasing ZNS doses [24]. In isolated cases, adding lamotrigine has been reported to increase the concentration of ZNS [25]. Therefore, the present study suggests that the effect of enzyme inducers on ZNS may be ambiguous. When clinicians encounter these situations and use ZNS as an add-on therapy to these anti seizure medicine, it should be titrated to the desired satisfactory effect.

Regarding safety, this study showed that ZNS was well-tolerated. Consistent with previous findings, our rate of AEs was 21.6%. Compared with Hamer et al. [14] and Dash et al. [15], the rates of AEs were 19.1% and 17.4%, respectively. In our study, the most frequent AEs were anorexia with weight loss (most of which was 15 kg), dizziness, headache, and lethargy; frequent agitation and mild rash were less frequent. No cases of kidney stones, metabolic acidosis, and oligohidrosis were reported. Most AEs were of mild to moderate intensity and did not involve death, disability, or hospitalization. Only 1.9% (2/102) of patients discontinued the drug due to headaches.

Our study had several limitations. First, we used PASS software (2021, version V21.0.3) to estimate the required sample size, which was 273 patients; however, we included 102 patients over an 8-month period for the following two reasons: first, we found that the frequency of seizures improved significantly after ZNS was used as an additional treatment; therefore, the results were deemed meaningful, and our follow up period was only for 5 months. Additionally, the conduct of clinical studies has been limited due to the impact of the COVID-19 outbreak. Second, without measuring ZNS and other drug serum levels, we could not accurately assess the effect of enzyme inducers on plasma levels associated with seizure control and AE. Third, urinary ultrasound examination was not performed before and after enrollment; therefore, the occurrence of kidney stones was unclear in this study.

5. Conclusion

Our findings confirm that ZNS is effective and well tolerated in both focal and sBTCS, suggesting that it is effective in various seizure types under real-life conditions due to its powerful broad-spectrum effects. In addition, our findings suggest that ZNS may be recommended for elderly patients with post-stroke epilepsy. In conclusion, our study is the first prospective multicenter real-world study conducted in China that supports the use of ZNS as the first additional treatment for focal or sBTCS with good therapeutic efficacy and tolerability.

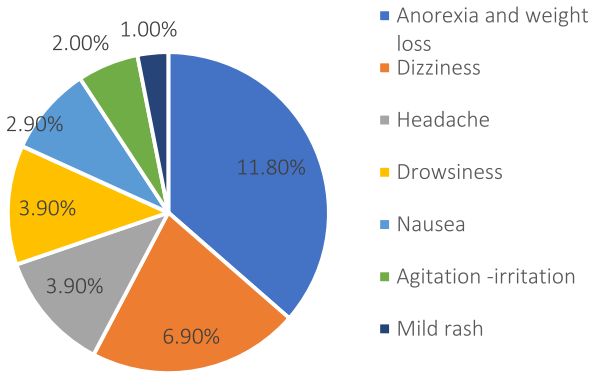

Fig. 4. Advers events associated with ZNS treatment.

Author contribution statement

Tingting Yang: Analyzed and interpreted the data; Wrote the paper.
Cuihua Yan, Yujiao Wu: Performed the experiments.
Tao Han, Xue wu Liu: Conceived and designed the experiments.
Huai kuan Wu, Junji Hu: Analyzed and interpreted the data.
Yang Jin, Jing Jiang: Contributed reagents, materials, analysis tools or data.

Funding statement

Mr Xue Wu Liu was supported by the National Natural Science Foundation of China [81873786].

Ethics statement

This study was approved by the ethics committee of Qilu Hospital of Shandong University, and the patients who participated in the study provided informed consent.

Data availability statement

The datasets [GENERATED/ANALYZED] for this study can be directed to the corresponding author/s.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

Special thank you for all the patients who participated in this study. Thanks to Xiqin Fang and Ranran Zhang of the research team for their drafting the article or critically revising its important intellectual content.

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