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ORIGINAL RESEARCH ARTICLE

Third-Generation Antiseizure Medication in the Treatment of Benzodiazepine-Refractory Status Epilepticus in Poststroke Epilepsy: A Retrospective Observational Register-Based Study

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Abstract

Background and Objective Status epilepticus in poststroke epilepsy is a challenging condition because of multiple vascular comorbidities and the advanced age of patients. Data on third-generation antiseizure medication (ASM) in this condition are limited. The aim of this study was to evaluate the efficacy of third-generation ASMs in the second- or third-line therapy of benzodiazepine-refractory status epilepticus in poststroke epilepsy following acute ischemic stroke.

Methods Data on the effectiveness of third-generation ASMs in patients with status epilepticus in poststroke epilepsy were gathered from two German Stroke Registries and the Mainz Epilepsy Registry. We included only cases with epilepsy remote to the ischemic event. No patients with acute symptomatic seizures were included. The following third-generation ASMs were included: brivaracetam, lacosamide, eslicarbazepine, perampanel, topiramate, and zonisamide. The assessment of effectiveness was based on seizure freedom within 48 h since the start of therapy with the respective ASM. Seizure freedom was evaluated both clinically (clinical evaluation at least three times per day) and by daily electroencephalogram records.

Results Of the 138 patients aged 70.8 ± 8.1 years with benzodiazepine-refractory status epilepticus in ischemic poststroke epilepsy, 33 (23.9%) were treated with lacosamide, 24 (17.4%) with brivaracetam, 23 (16.7%) with eslicarbazepine, 21 (15.2%) with perampanel, 20 (14.5%) with topiramate, and 17 (12.3%) with zonisamide. Seizure freedom within 48 h was achieved in 66.7% of patients with lacosamide, 65.2% with eslicarbazepine, 38.1% with perampanel, 37.5% with brivaracetam, 35.0% with topiramate, and 35.3% with zonisamide ($p < 0.05$ for comparison of lacosamide or eslicarbazepine to other ASMs).

Conclusions Based on these data, lacosamide and eslicarbazepine might be more favorable in the treatment of refractory status epilepticus in poststroke epilepsy, when administered as second- or third-line ASMs before anesthesia. Because of the fact that these ASMs share the same mechanism of action (slow inactivation of sodium channels), our findings could motivate further research on the role that this pharmaceutical mechanism of action has in the treatment of poststroke epilepsy.

Clinical Trial Registration This study was registered at ClinicalTrials.gov (NCT05267405).

1 Introduction

Owing to advances in stroke treatment, the mortality rate for patients with strokes has decreased substantially and the number of survivors after a stroke has increased worldwide [1]. However, they often survive with neurological sequelae [2]. Stroke is one of the most common causes of epilepsy in the elderly [3, 4]. In a pooled analysis of 34 longitudinal cohort studies, involving over 100,000 patients, the incidence rate for post-stroke seizures was about 7% and post-stroke epilepsy (PSE) was 5% [5]. In persons above 65 years of age, 30–49% of all new-onset epileptic seizures are due to PSE [6, 7]. In addition, PSE is associated with increased mortality in patients following a stroke [8]. The recurrence rate of epileptic seizures, that occur later than 7 days after stroke ("late seizures") is up to 71.5% [9, 10]. The diagnosis of PSE is therefore already made after the first late seizure and antiseizure medication (ASM) is indicated [11, 12].

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Key Points

Status epilepticus in poststroke epilepsy is challenging because of multiple vascular comorbidities and the advanced age of patients.

Lacosamide and eslicarbazepine might be more favorable in the treatment of refractory status epilepticus in poststroke epilepsy than brivaracetam, perampanel, topiramate, or zonisamide.

Slow inactivation of sodium channels is a mechanism of action that might be especially beneficial in the treatment of benzodiazepine-refractory status epilepticus in poststroke epilepsy.

Risk factors for developing PSE include younger age, acute symptomatic seizures, involvement of the cortex, involvement of middle or anterior cerebral artery territory, large lesions, severity of stroke, atherosclerotic etiology of ischemia, and hemorrhagic stroke [13–15]. Post-stroke epilepsy is an important clinical problem. About 33% of patients with PSE taking ASMs experience seizure recurrence within 1 year [10] and about 20% of patients with PSE develop benzodiazepine refractory seizures [16]. In particular, younger age at the time of stroke, type and severity of stroke, the occurrence of status epilepticus (SE), and seizure type have been identified as independent predictors for the development of therapy refractory PSE [16]. Recurrent seizures can lead to psychological stress, suppression of social activities, and thus to a decrease in recovery and quality of life for stroke survivors [17, 18].

However, the evidence for the treatment of PSE is limited. There are few studies to date investigating the efficacy and tolerability of ASMs in patients with PSE. Side effects and drug interactions must be taken into account, especially in older patients. Therefore, treatment with newer ASMs that do not induce enzymes may be beneficial [19]. Status epilepticus occurs in about 19% of patients admitted for a first-time seizure after a stroke [20]. It is an important and life-threatening clinical condition and there is a need to identify ASMs that would provide the most effective treatment of SE in PSE.

The second-line ASMs (i.e., after the failure of benzodiazepines to terminate SE), according to the national guidelines, are levetiracetam, valproate, and phenytoin/fosphenytoin [21]. If interruption of SE with ASMs has failed, anesthesia is the next step. However, in focal and non-convulsive SE, anesthesia could be postponed in order to reduce the risk of possible complications, and other ASMs could be applied as the second- and third-line therapy [21].

The aim of this study was to evaluate the efficacy of third-generation ASMs, which are used in the second- or third-line therapy of benzodiazepine-refractory SE in patients with PSE following acute ischemic stroke.

2 Methods

2.1 Study Design and Clinical Evaluation

The data on the effectiveness of third-generation ASMs in the second- and third-line ASM-therapy in patients with benzodiazepine-refractory SE in ischemic PSE were gathered from the Mainz Epilepsy Registry (MAINZ-EPIREG), Mainz Stroke Register (MAINZ-STREG), and the Marburg Stroke Register (MARSTREG). MARSTREG is a population-based stroke register that recruits all patients with acute ischemic stroke who are permanent residents in the district Marburg-Biedenkopf (Hessia, Germany, reference population 240,000 inhabitants). MAINZ-STREG is a stroke register recruiting all patients with acute ischemic stroke who are treated in the Department of Neurology of the University Medical Center Mainz, Germany. MAINZ-EPIREG is a population-based register of patients with epilepsy who are treated in the Mainz Comprehensive Epilepsy and Sleep Medicine Center (reference area of 4 million inhabitants). We included only cases with epilepsy remote to the ischemic event. No patients with acute symptomatic seizures were included.

The following third-generation ASMs were included: brivaracetam (SV2A selective agonist); lacosamide, and eslicarbazepine (both slow inactivation of sodium channels), perampanel (AMPA antagonist); topiramate (AMPA antagonist and carbonic anhydrase inhibitor); and zonisamide (sodium and calcium channel inhibitor and carbonic anhydrase inhibitor). Other third-generation ASMs were excluded because of the following reasons: 1. Levetiracetam is an early administered ASM in benzodiazepine-refractory SE and therefore it was not suitable for comparisons with ASMs applied at the later stages of treatment. 2. Rufinamide, retigabine, stiripentol, felbamate, vigabatrin, and fenfluramine are approved for specific epilepsy syndromes, such as Dravet, Lennox–Gastaut, or West syndromes, and therefore are not appropriate for comparisons in PSE. 3. Lamotrigine and cenobamate are not available for fast titration because of the risk of serious allergic reactions. 4. Data on gabapentin, pregabalin, tiagabine, and oxcarbazepine were not sufficient for a statistical analysis because of the very small number of patients ($n < 5$) in these groups.

Brivaracetam and lacosamide were administered intravenously. Eslicarbazepine, perampanel, topiramate, and zonisamide were administered via a nasogastric tube. We administered half of the maximal approved dose to initiate

the treatment with the corresponding ASM and doubled the dose on the next day, if SE was not interrupted. The initial dose and the maximal dose for different ASMs were as follows: brivaracetam (100 mg/day and 200 mg/day), eslicarbazepine (800 mg/day and 1600 mg/day), lacosamide (200 mg/day and 400mg/day), perampanel (6 mg/day and 12 mg/day), topiramate (250 mg/day and 500 mg/day), and zonisamide (250 mg/day and 500 mg/day).

Data collection was performed from 1 March, 2012 to 31 December, 2021. Once patients with benzodiazepine-refractory SE due to PSE had not responded to the next administered ASM, they were treated with the second- and third-line ASMs, under daily electroencephalogram controls and clinical evaluation. We would like to stress that we refer to a benzodiazepine-refractory SE, when we talk about second- or third-line therapy in the context of this paper. No co-administration of ASMs with the same mechanism of action took place in order to interrupt SE, for example, brivaracetam was not combined with levetiracetam, or lacosamide with phenytoin. If refractory SE could not be interrupted by the last administered second- or third-line ASM, intravenous anesthesia was given. In all included cases, the evaluated drugs were administered as the last ASM prior to cessation of SE or prior to initiation of anesthesia.

The assessment of effectiveness was based on seizure freedom achieved within 48 h since the start of therapy with the respective ASM. Seizure freedom was evaluated both clinically (clinical evaluation at least three times per day) and by daily electroencephalogram records. The clinical parameters included demographics, SE severity score, ASM, duration of SE, electroencephalogram data, and comorbidities.

This study was approved by the local ethics committee (State Medical Association Rheinland-Pfalz) and all patients signed an informed consent for participation in this study. This study has been registered at ClinicalTrials.gov with the registration number NCT05267405.

2.2 Statistics

The statistical analysis was performed using IBM SPSS Statistics Version 23.0 (IBM Corp., Armonk, NY, USA). The data are presented as mean and standard deviation (SD) or median and range. A *t*-test was applied for comparisons of normally distributed variables. If data were not normally distributed, the Mann–Whitney *U*-test (two independent groups) was used. The Kruskal–Wallis test (numerical variables) and Fisher's exact test (categorical variables) were applied for group comparisons between different ASMs in Table 2. The post hoc test results (Dunn's test for numerical variables and pairwise Fisher's exact test with Benjamini-Hochberg correction for categorical variables) are also presented in Table 2. Statistical significance was assumed at a p-value of <0.05.

Logistic regression analysis with forward selection ($p < 0.1$) was performed to identify independent factors affecting control of SE. These data are presented as odds ratios and 95% confidence intervals.

3 Results

A total of 138 patients with SE in PSE were included. Of these, 67 patients (48.6%) were female, 33 (23.9%) were treated with lacosamide, 21 (15.2%) with perampanel, 24 (17.4%) with brivaracetam, 23 (16.7%) with eslicarbazepine, 20 (14.5%) with topiramate, and 17 (12.3%) with zonisamide. Our study enrolled approximately 80% of patients treated because of SE in PSE in recruiting centers. The remaining 20% did not receive third-generation ASMs to interrupt SE.

Data on demographics and clinical parameters are shown in Table 1. The average age of patients was 70.8 ± 8.1 years. The average time span between stroke and the onset of epilepsy was 5.1 ± 2.9 years. The largest proportion of patients with PSE were initially treated with levetiracetam (39.1%), followed by lamotrigine (28.3%) and valproic acid (14.5%). Status epilepticus occurred a mean of 2.7 ± 1.6 years after the diagnosis of epilepsy. Focal motor presentation of SE was observed in 81 patients (58.7%). Non-convulsive SE was diagnosed in 57 patients (41.3%). On average, 2 days had elapsed since the onset of SE until the administration of one of the above-mentioned ASMs. In terms of common co-morbidities, 101 patients (73.2%) had arterial hypertension, 86 (62.3%) had hyperlipidemia, and 39 (28.3%) had diabetes mellitus. In addition, 33 (23.9%) were smokers and 62 (44.9%) had atrial fibrillation as a cardiovascular risk factor. The stroke occurred in the right hemisphere of the brain in half of the patients and in the left hemisphere in the other half of the patients.

Overall, in 67 of 138 patients (48.6%), the SE was interrupted within 48 h of the initiation of the third-generation second- or third-line ASM. This was achieved in 66.7% with eslicarbazepine therapy, in 65.2% with eslicarbazepine, in 38.1% with perampanel, in 37.5% with brivaracetam, 35.3% with zonisamide, and in 35.0% with topiramate ($p < 0.05$ for the comparison of lacosamide or eslicarbazepine to other ASMs, Table 2).

No serious adverse side effects were observed during the hospital stay. Among last received ASM, both ASMs acting via the slow inactivation of sodium channels (eslicarbazepine and lacosamide) were identified as independent predictive factors of status control in a logistic regression analysis (Table 3). Brivaracetam and perampanel showed a trend but did not reach the level of statistical significance because

Table 1 Data on demographics and clinical parameters of patients with PSE and SE

	Patients with PSE and SE ($N = 138$)
Age, years	
Mean (±SD)	70.8 (±8.1)
Sex, *n* (%)	
Male	71 (51.4)
Female	67 (48.6)
Days of SE prior to last ASM[a]	
Mean (±SD)	2.1 (±0.8)
Duration of SE (days)	
Mean (±SD)	4.4 (±1.4)
Number of previous ASMs	
Mean (±SD)	2.2 (±0.7)
STESS	
Mean (±SD)	2.5 (±0.9)
Control of SE, *n* (%)	
Yes	67 (48.6)
No	71 (51.4)
Risk factors, *n* (%)	
Arterial hypertension	101 (73.2)
Hyperlipidemia	86 (62.3)
Diabetes mellitus	39 (28.3)
Smoking	33 (23.9)
Atrial fibrillation	62 (44.9)
Affected hemisphere, *n* (%)	
Right	68 (49.3)
Left	70 (50.7)

ASM antiseizure medication, *PSE* poststroke epilepsy, *SD* standard deviation, SE status epilepticus, *STESS* status epilepticus severity score

[a]Number of days in SE prior to administration of the last ASM, which either interrupted SE or after which anesthesia was initiated

their ORs included 1. The other independent predictors of status control were the days of SE before the start of the new ASM, the number of previous ASMs, and the absence of two cardiovascular risk factors (smoking and atrial fibrillation). The other variables, such as age, sex, SE severity score, and other risk factors were not among the independent predictors of SE termination (Table 3).

4 Discussion

Until now, only a few studies have focused on the treatment of PSE; therefore, the evidence for the treatment of SE in PSE is limited. This study demonstrated that in 48.6% of patients with PSE, the benzodiazepine-refractory SE was successfully interrupted within 48 h by administration of one of the third-generation ASMs as the second- or third-line therapy.

Our findings show advantages of lacosamide and eslicarbazepine in the treatment of SE in PSE. One can speculate that the common mechanism of action of lacosamide and eslicarbazepine, in the form of enhancement of slow inactivation of voltage-gated sodium channels, could be an explanation for the benefits. The more prominent influence on seizure frequency in PSE compared with other mechanisms of action was already shown for ASMs acting via slow inactivation of sodium channels in our recent study [22].

Differences in pharmacokinetics between investigated ASMs is an important issue in the treatment of SE. Brivaracetam and lacosamide are administered intravenously and have a half-life of 7–13 h [23, 24]. Eslicarbazepine, topiramate, perampanel, and zonisamide are only available for oral administration and have longer half-lives of 20–24 h, 19–25 h, 85–105 h, and 63–69 h, respectively [25–29]. Because of the fact that the steady state of ASMs with a longer half-life is achieved several days after the treatment initiation (expected time of steady state is approximately five times longer than the half-life), loading doses of corresponding ASMs are necessary [25]. The administration of half of the maximal approved dose to start the treatment and its doubling on the following day appeared to be an effective approach for SE interruption.

In previous studies, there is already some evidence that the treatment of PSE with third-generation ASMs may be beneficial. Both better efficacy and better tolerability than with previous generations of ASMs were shown [30]. For example, monotherapy with lamotrigine showed significantly lower mortality compared with carbamazepine, and levetiracetam was shown to have a reduced risk of cardiovascular death compared with carbamazepine [19]. So far, there are very few explicit studies on the treatment of PSE with lacosamide. One recent study investigated the efficacy and tolerability of therapy with lacosamide compared to therapy with carbamazepine in 61 patients with cerebrovascular epilepsy [31]. Treatment with lacosamide resulted in a higher seizure-free rate than with carbamazepine. After 3 months, monotherapy with lacosamide showed a response in 80% of patients and an absence of seizures in 56%. In addition, a lower side-effect profile was observed, especially with unaffected lipid concentrations. In our recent study, lacosamide was favorable in the treatment of PSE compared with ASMs having other mechanisms of action [22].

There are already several studies on the treatment of SE with lacosamide, which report control of SE in 50–82.4% of patients within 12–48 h [32–35]. Some studies on the treatment of SE with lacosamide were also able to show that an earlier start of therapy involved a higher efficacy [36, 37]. In the present study, the increased number of days before starting the new ASM and the amount of ASMs

Table 2 Clinical parameters of patients with poststroke epilepsy and SE analyzed based on ASMs

	Brivaracetam (*n* = 24)	Lacosamide (*n* = 33)	Perampanel (*n* = 21)	Eslicarbazepine (*n* = 23)	Topiramate (*n* = 20)	Zonisamide (*n* = 17)	*p*-value
Age, years, mean (±SD)	71.0 (±8.1)	71.6 (±9.0)	70.7 (±7.5)	69.5 (±9.1)	70.3 (±7.8)	71.2 (±6.4)	0.948
Sex, *n* (%)							
Male	13 (54.2)	17 (51.5)	11 (52.4)	10 (43.5)	11 (55.0)	9 (52.9)	0.979
Female	11 (45.8)	16 (48.5)	10 (47.6)	13 (56.5)	9 (45.0)	8 (47.1)	
Days of SE before start of new ASM, mean (±SD)	2.0 (±0.8)	1.9 (±0.9)	2.4 (± 0.7)	2.0 (± 0.8)	2.1 (± 0.8)	2.5 (± 0.7)	0.302
Control of SE, *n* (%)	9 (37.5)[a,e]	22 (66.7)[a,b,c,d]	8 (38.1)[b,f]	15 (65.2)[e,f,g,h]	7 (35.0) [c, g]	6 (35.3) [d, h]	0.031
Number of previous ASMs, mean (± SD)	1.3 (± 0.6)	1.0 (± 0.8)	1.4 (± 0.7)	1.4 (± 0.7)	1.3 (± 0.7)	1.4 (± 0.5)	0.244
STESS, mean (± SD)	2.4 (± 0.9)	2.6 (± 0.8)	2.7 (± 0.8)	2.3 (± 1.0)	2.4 (± 0.9)	2.5 (± 0.6)	0.739

ASM antiseizure medication, *SD* standard deviation, *SE* status epilepticus, *STESS* status epilepticus severity score

[a]Statistically significant difference at $p < 0.05$ between lacosamide and brivaracetam

[b]Statistically significant difference at $p < 0.05$ between lacosamide and perampanel

[c]Statistically significant difference at $p < 0.05$ between lacosamide and topiramate

[d]Statistically significant difference at $p < 0.05$ between lacosamide and zonisamide

[e]Statistically significant difference at $p < 0.05$ between eslicarbazepine and brivaracetam

[f]Statistically significant difference at $p < 0.05$ between eslicarbazepine and perampanel

[g]Statistically significant difference at $p < 0.05$ between eslicarbazepine and topiramate

[h]Statistically significant difference at $p < 0.05$ between eslicarbazepine and zonisamide

Table 3 Logistic regression analysis of the control of SE in patients with poststroke epilepsy

	OR	95% CI
Age	0.921	0.839; 1.010
Female sex	5.189	0.984; 27.352
Days of SE prior to last ASM	**0.017**	**0.002; 0.117**
Number of previous ASMs	**0.067**	**0.012; 0.374**
Vascular risk factors		
Diabetes mellitus	0.307	0.048; 1.956
Smoking	**0.180**	**0.024; 0.987**
Atrial fibrillation	**0.156**	**0.016; 0.948**
ASM		
BRV	5.137	0.883; 29.898
ESL	**6.749**	**1.074; 15.393**
LCM	**8.107**	**2.014; 21.808**
PER	5.320	0.795; 35.581

ASM antiseizure medication, *BRV* brivaracetam, *CI* confidence interval, *ESL* eslicarbazepine, *LCM* lacosamide, *OR* odds ratio, *PER* perampanel, *SE* status epilepticus

Only variables that fulfilled the criterion of $p < 0.01$ in terms of forward selection were included in this model

previously used were also identified as negative independent predictors of SE control. There is only one previous study on the treatment of non-convulsive SE in PSE with lacosamide [38]. In this study, intravenous treatment with lacosamide resulted in the termination or significant reduction of epileptic activity after 45–60 min in 50% of patients (8 of 16). No side effects were observed.

To our knowledge, no studies have been performed on the treatment of SE in PSE with eslicarbazepine. The evidence for the treatment of PSE with eslicarbazepine is currently limited. However, the recent evidence shows its advantages in the treatment of PSE [22]. In one study, as in the present study, a significantly higher response rate and the absence of seizures were shown in patients with PSE than in patients with other types of epilepsy when treated with eslicarbazepine [39]. Inhibition of epileptogenesis and attenuated neuronal loss were shown for the treatment of SE with eslicarbazepine in animal models [40, 41]. However, this needs to be further investigated in subsequent studies.

Another interesting finding of our study is that smoking and the presence of atrial fibrillation were identified as independent negative predictors regarding the control of SE.

Atrial fibrillation is often associated with a worse neurological outcome [42], as well as a larger volume of infarction and cortex involvement, which in turn are all risk factors for PSE [13] and the development of SE. For smokers with epilepsy, some studies have already shown an increased risk of seizures compared with non-smokers with epilepsy [43, 44]. An increased risk of refractory epilepsy has not been shown [44]. However, smoking could be related to the severity of epilepsy [44]. One possible cause could be the direct effect of nicotine on glutamate secretion [43]. Another possible cause could be the proinflammatory effect of smoking. It has already been shown that inflammatory mechanisms play a major role both after a stroke and in epileptogenesis [45]. These processes are possibly further intensified by smoking. However, additional prospective studies are needed to investigate this association.

Among the limitations of this study were its observational design, implying that the evidence could not be provided at the level of randomized controlled trials. Status epilepticus is a challenging condition complicating the recruitment of patients. Nevertheless, 138 patients could be enrolled, which makes the present study very large in comparison to research efforts undertaken for this indication so far. Unfortunately, a subgroup analysis of concomitant medication could not be performed because of the small numbers of patients in these subgroups. Additionally, residual confounding by unmeasured variables could not be excluded in a logistic regression analysis. Such variables include neurological status in the last weeks prior to SE, interictal epileptiform discharges prior to SE, and compliance to ASM. We do not expect bias in the results because of the absence of these variables in our analysis but there could be other factors determining the probability of SE control.

5 Conclusions

We provide the data showing that lacosamide and eslicarbazepine might be more favorable than other third-generation ASMs in the treatment of benzodiazepine-refractory SE in PSE, when they are administered as second- or third-line ASMs before anesthesia. The slow inactivation of sodium channels is the mechanism of action of lacosamide and eslicarbazepine may have beneficial effects in the treatment of this etiological entity of SE. Our data should motivate further studies, specifically randomized controlled trials, investigating third-generation ASM in this relevant clinical condition.

Declarations

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Conflicts of Interest/Competing Interests Yaroslav Winter reports honoraria for educational presentations and consultations from Arvelle Therapeutics, Bayer AG, BIAL, Eisai, LivaNova, Novartis, and UCB Pharma. Sergiu Groppa received compensation for professional services from Abbott, Abbvie, Bial, Medtronic, UCB, and Zambon; research grants from Abbott, Boston Scientific, MagVenture, German Research Council, Innovations Fund, and the German Ministry of Education and Health. Katharina Sandner, Thomas Vieth, Gabriel Gonzalez-Escamilla, and Sebastian V. Stuckrad-Barre have no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval This study was approved by the local ethics committee [State Medical Association Rheinland-Pfalz, Reference number: 837.560.17 (11394)].

Consent to Participate All patients signed an informed consent for participation in this study.

Consent for Publication Not applicable.

Availability of Data and Material The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code Availability Not applicable.

Authors' Contributions Conceptualization and design: YW, SG. Methodology and data collection: YW, KS, SSB, SG. Analysis and interpretation: YW, KS, TV, GGE, SG. Writing, original draft preparation: YW, KS, TV, SG. Writing, reviewing, and editing: YW, KS, TV, SSB, GGE, SG. All authors have read and approved the final submitted manuscript, and agree to be accountable for the work.

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