Oxcarbazepine oral suspension in pediatric patients with partial seizures and/or generalized tonic-clonic seizures: a multi-center, single arm, observational study in China

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Background: **To assess efficacy and safety of oxcarbazepine (OXC) oral suspension in pediatric patients aged 2-16 years with partial seizures (PS) and/or generalized tonic-clonic seizures (GTCS) in real-world clinical practice in China.**

Methods: **This 26-week, single arm, multicenter and observational study recruited patients aged 2-16 years with PS or GTCS suitable for OXC oral suspension treatment. Enrolled patients received OXC oral suspension treatment for 26 weeks. Primary endpoints included mean seizure frequency at the end of the treatment and mean seizure frequency reduction at the end of the treatment *vs.* baseline. Secondary efficacy-related endpoints and safety parameters were also assessed.**

Results: **Nine hundred and eighty-seven pediatric patients were enrolled and 912 (92.4%) completed the study. The mean seizure frequencies at baseline and the end of week 26 were 13.40±64.92 and 1.62±19.47 times/month, respectively. The mean seizure frequency reduction was 10.03±63.67 times/month and the mean seizure frequency reduction percentage was 90.02%±5127.0% (P<0.0001). After 26 weeks of treatment, 82.36%, 7.24% and 3.86% of the patients became controlled, significantly improved and improved, respectively. Adverse events (AEs) were reported in 74 (7.65%) patients. Rash was the most common AE. The efficacy of OXC was not affected by seizure types, age or gender.**

Conclusion: **This study confirms the efficacy and good safety profile of OXC oral suspension in Chinese pediatric patients aged 2-16 years with PS and/or GTCS.**

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Key words: **children;**
efficacy;
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Introduction

Epilepsy is a common chronic neurological disorder affecting 10 million children worldwide. Its estimated prevalence is approximately 0.5%-1% in children ≤16 years of age, and an estimated 20 000 to 45 000 new cases of pediatric epilepsy are diagnosed annually.[1-4] In China, pediatric epilepsy has an estimated prevalence of 0.33%-0.68%.[5,6] Successful epilepsy treatment in children remains a challenge, more than 25% of children with epilepsy have treatment-refractory seizure and cannot maintain long-term seizure freedom.[4,7]

Identifying a proper treatment for pediatric patients is particular challenging due to limited efficacy and safety data on this population. Additionally, pediatric and adult patients have different pharmacological, efficacy and safety profiles.[2] Although effectiveness of the first-generation antiepileptic drugs (AEDs) such

as carbamazepine, valproate and phenytoin is well established, there have always been concerns about their long-term safety and tolerability in children.[1,2,8,9]

The second-generation AED oxcarbazepine (OXC) is a keto-analog of carbamazepine designed to overcome the toxicity, auto-induction and drug-interaction profile associated with carbamazepine.[2,10,11] OXC monotherapy or adjunctive therapy is indicated for treating partial seizure (PS) in adults and in children 4 years of age in the United State and 2 years of age in China, and it is currently the only AED with Class I evidence and Level A recommendation for efficacy in children with PS monotherapy.[12-14] Various studies have demonstrated its efficacy in seizure control and its good safety profile.[2,15-18] OXC administered in the form of oral suspension allows for more accurate dosing and easier pediatric administration compared to tablet and therefore is considered a better option.[18] Despite studies reporting the efficacy and safety of OXC in treating pediatric epilepsy,[2,7,15-24] only a few small-scale studies evaluated OXC in Chinese pediatric patients with PS.[14,18,25,26] In a large-scale, multi-center, single-arm, open-label and observational study, we evaluated the efficacy and safety of OXC monotherapy or adjunctive therapy in 606 Chinese pediatric patients aged 2-5 years with PS and/or generalized tonic-clonic seizures (GTCS) in real-world clinical practice in China.[27] After 26 weeks of OXC treatment, compared to baseline, 81.8%, 7.0% and 4.5% of the patients achieved 100% seizure frequency reduction, ≥75% but less than 100% seizure frequency reduction and ≥50% but less than 75% seizure frequency reduction, respectively. Adverse events (AEs) were observed in 49 (8.1%) patients, with rash [18 (2.97%)] being the most common AE. That study confirmed the efficacy and safety of OXC oral suspension in Chinese pediatric patients aged 2-5 years with PS and/or GTCS in real-word clinical practice.

There has been very little efforts in exploring how age impacts efficacy and safety of OXC, especially in pediatric patients. Only one study assessed whether OXC oral suspension had different efficacy and safety profiles in infants (<1 year) and children (1-9 years old).[18] It found that OXC oral suspension had comparable efficacy and tolerability in infant and children.[18] On the other hand, studies on other AEDs reported that age could impact the efficacy and safety of AEDs such as topiramate.[28,29] Kholin et al[28] divided 722 patients with epilepsy aged from 3 months to 57 years into 3 age-based groups: <1 year, 1-3 years and >3 years, and found that the efficacy of topiramate increased and the risk of seizure aggravation decreased as the age increased. Additionally, Voronkova et al[29] found that the efficacy of topiramate was higher in adolescents, youths and adults than in younger children. Furthermore, it has been reported that age was a factor affecting the degree of drug interactions of AEDs such as lamotrigine in children and adolescents.[30] Finally, studies found that young children (aged 2-5 years) needed higher dose of OXC than older children (aged 6-12 years) because young children had more rapid OXC clearance, therefore an increase in the daily dose of OXC by up to 30% in children aged 2-5 years has been recommended.[31,32] These studies suggested that younger children (aged 2-5 years) belonged to a special age group in terms of AED dosing, and as we know, dosing may affect efficacy and safety. Based on these findings, we extended the range of ages of eligible pediatric patients and conducted the current study on the efficacy and safety of OXC oral suspension in Chinese children of 2-16 years of age with PS and/or GTCS in real-world clinical practice in China. The study was a large-scale, 26-week, multi-center, single-arm, open-label and observational study. Subgroup analysis was conducted based on age ("≥2 years and <5 years" and "≥5 years and <16 years") to investigate whether age impacted the efficacy and safety of OXC. Additional subgroup analyses based on patients' type(s) of seizure and gender were also conducted to further examine the efficacy of OXC in more detail.

Methods

Patients

Pediatric patients aged 2-16 years with previously confirmed diagnosis of PS and/or GTCS were included in this study if they had not received OXC treatment within 30 days prior to enrollment and were judged to be suitable for OXC therapy by their physicians. Key exclusion criteria included the presence of generalized seizures other than GTCS or the presence of febrile convulsion, known intolerance/poor response to OXC treatment, or the presence of any severe/unstable condition(s) unsuitable for the study as judged by their attending physicians. Patient(s) included in our other large-scale, multi-center, single-arm, open-label and observational study[27] were also excluded.

Ethics

Informed consent was obtained from patients' legal representative and patients were enrolled after their eligibility assessment. This study was approved by the Independent Ethics Committees or Institutional Review Board of each study center, and was conducted according to the ethical principle of the Declaration of Helsinki.[33] Its State Food and Drug Administration approval number is 2008S03406.

Study design

In this 26 week, single arm, open label, multi-center,

observational and post marketing surveillance study (protocol No. CTRI476BCN04) conducted between 15 June 2009 and 20 March 2011, patients received OXC oral suspension treatment as per routine clinical practice of their attending physicians. Baseline demographic information, current medical condition and medical history were recorded at baseline visit. Physical examination, laboratory examination, electroencephalogram (EEG), OXC administration, concomitant medications along with the study-related efficacy and safety parameters were monitored and recorded at baseline visit and weeks 4, 13 and 26.

Patients were recruited from 23 medical centers in China and received OXC oral suspension treatment (trileptal oral suspension, 250 mL/bottle containing OXC 60 mg/mL, Novartis Pharma S.A.S., Switzerland) for 26 weeks according to the approved package insert and as per the physicians' routine practice. Treatment was initiated with a dose of 8-10 mg/kg/day given in two doses as monotherapy or adjunctive therapy. If clinically indicated, the dose could be increased by a maximum of 10 mg/kg at weekly intervals to a maximum dose of 60 mg/kg/day as long as the patients could tolerate it. Concomitant medications were allowed.

Efficacy endpoints

Primary efficacy endpoints included mean seizure frequency at the end of the 26-week treatment and mean seizure frequency reduction at the end of the treatment compared to baseline [difference between baseline and end-of-treatment seizure frequency (times/month)]. Secondary efficacy endpoints included: 1) mean seizure frequency reduction percentage at week 26 compared to baseline; 2) the percentage of patients who became controlled (100% seizure frequency reduction at week 26) (seizure frequency at week 26 was defined as the average number of seizure episodes per month between week 26 and the previous visit; baseline seizure frequency was the average number of seizure episodes per month within 3 months prior to enrollment in the study; and seizure frequency reduction at week 26 was defined as baseline seizure frequency-seizure frequency at week 26/baseline seizure frequency), significantly improved (≥75% but less than 100% seizure frequency reduction), improved (≥50% but less than 75% seizure frequency reduction), no change or worsening (<50% seizure frequency reduction); 3) retention rate (the percentage of patients who completed the study).

Subgroup analyses based on age (2≤age<5 years and 5≤age<16 years), seizure types [simple partial seizure (sPS), complex partial seizure (cPS), partial seizure with secondary generalization (PSSG) and GTCS] and gender were also conducted.

In addition, average initial dosage, average maintenance dosage and time to achieve the maintenance dosage were also monitored and recorded.

Safety endpoints

Incidence of AEs and serious AEs (SAEs), their severities and possible relationships to OXC treatment were monitored and recorded at each visit.

Statistical analysis

Analyses of baseline demographics, disease characteristics, efficacy endpoints and also subgroup analyses were performed on all patients who received at least 1 dose of OXC and had at least one post-baseline efficacy assessment [full analysis set (FAS)] with last observation carried forward. Secondary population for supportive analysis included all FAS patients who had no pre-specified protocol violation during the study [per protocol set (PPS)]. Safety analysis was performed on all patients who received at least one dose of OXC and had at least one post-baseline safety assessment [safety set (SS)]. Descriptive statistics was used to analyze the study parameters. SAS 9.1.3 (TS1M3) for Windows was used for all statistical analyses. All statistical tests were conducted against a two-sided alternative hypothesis with a significance level of 0.05.

Results

Patient demographics and baseline characteristics

A total of 987 patients from 23 medical centers in China were enrolled in the study, among them, 912 (92.4%) patients completed the 26-week study (Fig. 1); and 75 (7.60%) patients withdrew from the study, AE (22, 2.23%), poor efficacy (18, 1.82%) and lost to follow-up (12, 1.22%) as the most common reasons (Fig. 1). The FAS, PPS and SS consisted of 932, 857 and 967 patients, respectively (Fig. 1). Thirty-one of the 967 patients in the SS received OXC treatment for less than four weeks and did not have any post-baseline safety assessment before their withdrawal from the study, and four other patients had only one post-baseline safety

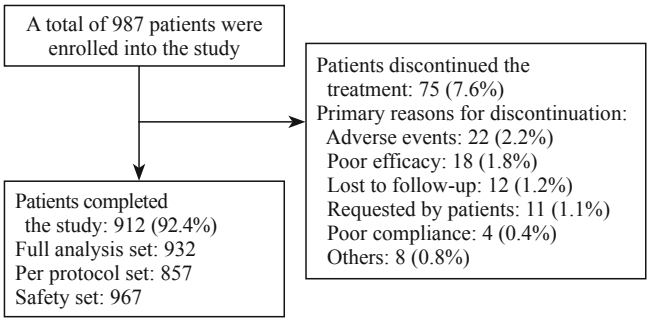

Fig. 1. Flow diagram of the included patients.

assessment without any efficacy assessment, these 35 patients were therefore not included into the FAS.

Patients' mean age was 5.19 years, mean weight was 19.56 kg, and 58.37% of the patients were male (Table 1). Of the 932 FAS patients, 515 were aged ≥2 years and <5 years, and the rest 417 were ≥5 years and <16 years. Their mean epilepsy duration at baseline was 11.73 months and mean baseline seizure frequency (times/month) was 13.40. PSSG was the most common type of seizure, presented in 56.01% of the patients, followed by sPS (31.22%), GTCS (14.48%) and cPS (2.90%). Distributions of the four seizure types within the two age-based subgroups were well balanced (Table 1). Concomitant medications used by the patients are listed in Table 1.

Table 1. Demographic, baseline characteristics of the patients (*n*=932) and concomitant medication used (*n*=967)

Items	Values
Demographics	
Age (y), mean±SD (range)	5.19±2.80 (2.00-15.08)
Age-based subgroups (y), *n* (%)	
2≤age<5	515 (55.26)
5≤age<16	417 (44.74)
Gender male/female, *n* (%)	544 (58.37)/388 (41.63)
Weight (kg), mean±SD (range)	19.56±8.45 (7-75)
Disease duration (mon), mean±SD (range)	11.73±17.71 (0-63)
Seizure frequency per mon, mean±SD	13.40±64.92
Classification of seizure types*, *n* (%)	
Partial seizure with secondary generalization	522 (56.01)
Complex partial seizure	27 (2.90)
Simple partial seizure	291 (31.22)
Generalized tonic-clonic seizures (primary)	135 (14.48)
Classification of seizure types based on age* (y), *n* (%)	
Partial seizure with secondary generalization	
2≤age<5	287 (55.73)
5≤age<16	235 (56.35)
Complex partial seizure	
2≤age<5	14 (2.72)
5≤age<16	13 (3.12)
Simple partial seizure	
2≤age<5	159 (30.87)
5≤age<16	132 (31.65)
Generalized tonic-clonic seizures (primary)	
2≤age<5	79 (15.34)
5≤age<16	56 (13.43)
Concomitant medication, *n* (%)	
Central nervous system drugs	177 (18.30)
Valporate	100 (10.34)
Topirmate	56 (5.79)
Levetiracetam	48 (4.96)
Lamotrigine	15 (1.55)
Phenobarbital	10 (1.03)
Nitrazepam	6 (0.62)
Clonazepam	5 (0.52)
Carbamazepine	4 (0.41)
Phenytoin	1 (0.10)

*: Some patients had multiple types of seizure and as such, they were included in multiple seizure-type based subgroups. SD: standard deviation.

Efficacy

The FAS population of 932 patients was used for efficacy assessment. Their mean baseline seizure frequency was 13.40±64.92 times/month, and at the end of the 26-week OXC treatment, mean seizure frequency was reduced to 1.62±19.47 times/month, reflecting a significant mean seizure frequency reduction of 10.03 63.67 times/month and a mean seizure frequency reduction percentage of 90.0%±5127.0% (P<0.0001) (Table 2). Further, after 26 weeks of OXC treatment, the percentages of patients who became controlled, significantly improved, improved, and no change or worsening were 82.36%, 7.24%, 3.86%, and 6.54%, respectively (Fig. 2).

Subgroup analysis showed that OXC treatment demonstrated comparable efficacy in patients of the "2≤age<5" group (*n*=515) and the "5≤age<16" group (*n*=417). Patients in the "2≤age<5" group and the "5≤age<16" group had mean baseline seizure frequencies of 12.46±55.70 and 14.55±74.79 times/month that were significantly reduced to 0.46±2.73 and 3.00±28.66 times/month at the end of the 26-week

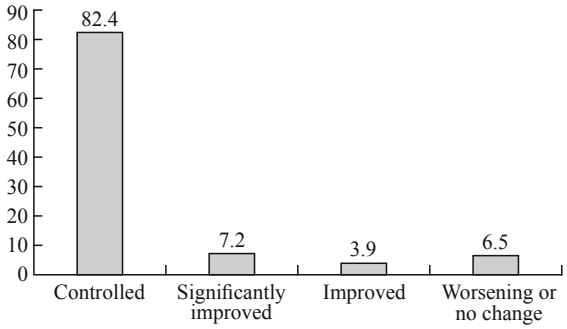

Fig. 2. Percentages of patients reaching pre-specified seizure frequency reduction percentages at week 26 (full analysis set, last observation carried forward). Controlled: 100% seizure frequency reduction; Significantly improved: ≥75% but less than 100% seizure frequency reduction; Improved: ≥50% but less than 75% seizure frequency reduction; No change or worsening: <50% reduction at week 26 compared to baseline.

Table 2. Seizure frequency and seizure frequency reduction percentage (full analysis set, last observation carried forward) (*n*=932)

Visits	*n* (missing)	Seizure frequency (times/mon), mean±SD	Mean seizure frequency reduction (from baseline) (times/mon), mean±SD	Mean seizure frequency reduction percentage (from baseline), mean±SD	*P* value*
Baseline	931 (1)	13.40±64.92	-	-	-
End of Week 4	932 (0)	4.54±22.29	-8.85±61.22	35.85±309.09	<0.0001
End of Week 13	886 (46)	2.01±19.50	-9.92±61.55	73.99±107.90	<0.0001
End of Week 26	863 (69)	1.62±19.47	-10.03±63.67	90.02±5127.0	<0.0001

*: *P* value was calculated with the Wilcoxon signed-rank test. "-": no data. SD: standard deviation.

OXC treatment, respectively (P<0.0001 and 0.0002, respectively). Further, 391 (84.09%), 34 (7.31%) and 14 (3.01%) patients in the "2≤age<5" group, and 314 (80.31%), 28 (7.16%) and 19 (4.86%) patients in the "5≤age<16" group became controlled, significantly improved, and improved, respectively (Table 3). Analysis on the PPS population supported the FAS results.

In addition, OXC was efficacious for all the four seizure types (sPS, cPS, PSSG and GTCS) presented in this study. It led to significant reduction of mean seizure frequency from baseline at the end of the 26-week OXC treatment for all the four types of seizure (P<0.0001 for all). In addition, 221 (84.03%), 23 (8.75%) and 8 (3.04%) patients with sPS become controlled, significantly improved and improved, respectively; 22 (91.67%), 1 (4.16%) and 0 (0.00%) patients presented with cPS were controlled, significantly improved and improved, respectively; 391 (81.12%), 35 (7.27%) and 22 (4.56%) patients with PSSG were controlled, significantly improved and improved, respectively; as for patients with GTCS, 97 (78.23%), 12 (9.68%) and 5 (4.03%) became controlled, significantly improved and improved, respectively. Finally, OXC demonstrated comparable efficacies in male and female patients (data not shown). The PPS results were consistent with the FAS results.

Nine hundred and twelve (92.4%) of the 987 enrolled patients completed the study, indicating a retention rate of 92.4%.

Table 3. Adverse events (safety set) (n=967)

Variables	n (%)/cases
Total	74 (7.65)/105
Skin and subcutaneous disorders	33 (3.41)/34
Rash	32 (3.31)/33
Itching	1 (0.10)/1
Nervous system disorders	23 (2.38)/24
Somnolence	8 (0.83)/8
Myoclonus	6 (0.62)/6
Fatigue	4 (0.41)/4
Headache	1 (0.10)/1
Learning disability	1 (0.10)/1
Movement disorder	1 (0.10)/1
Tremor	1 (0.10)/1
Seizure	1 (0.10)/1
Muscle contract	1 (0.10)/1
Gastrointestinal disorders	13 (1.34)/19
Nausea	4 (0.41)/5
Disgusting	4 (0.41)/4
Stomach pain	3 (0.31)/3
Stomach uncomfortable	3 (0.31)/3
Vomiting	2 (0.21)/2
Constipation	1 (0.10)/1
Mouth ulcer	1 (0.10)/1
General disorders	8 (0.83)/8
Fever	5 (0.52)/5
Fatigue	2 (0.21)/2
Varicella	1 (0.10)/1
Respiratory disorders	4 (0.41)/4
Upper respiratory tract infection	4 (0.41)/4
Others	4 (0.41)/4
Overdose	3 (0.31)/3
Trauma	1 (0.10)/1
Hepatobiliary disorders	2 (0.21)/4
Alanine aminotransferase increased	2 (0.21)/2
Abnormal liver function test	1 (0.10)/1
Aspartate aminotransferase increased	1 (0.10)/1
Immune system disorders	3 (0.31)/3
Allergy	2 (0.21)/2
Infection	1 (0.10)/1
Musculoskeletal and bone disorders	1 (0.10)/1
Arthralgia	1 (0.10)/1
Eye disorders	1 (0.10)/2
Visual disorder	1 (0.10)/2

Safety and tolerability

The SS population (n=967) was used for safety analysis. OXC treatment was started with a mean initial dose of 10.62±3.99 mg/kg/day (median: 9.60 mg/kg/day, range: 2.40-40.50 mg/kg/day) which was then titrated up to a mean maintenance dose of 25.20±10.49 mg/kg/day (median: 24.62 mg/kg/day, range: 5.00-80.00 mg/kg/day). The average number of days needed to achieve the maintenance dose was 40.12±34.73 days (median: 28.00 days, range: 7.00-154.00 days).

Seventy-four (7.65%) patients reported a total of 105 cases of AEs, of them, 75 cases experienced by 57 patients were suspected to be treatment-related. Most of the AEs were mild and transient. One patient experienced one SAE (rash) and recovered after discontinuation of the OXC treatment and symptomatic treatment. The most common AEs included skin and subcutaneous tissue disorders, nervous system disorders and gastrointestinal disorders (Table 3). By symptoms, rash (3.31%), somnolence (0.83%), myoclonus (0.62%) and fever (0.52%) were the four most common AEs. Overall, 22 (2.23%) patients withdrew from the study due to AEs. No death occurred during the study and no new safety concerns were flagged.

Subgroup analysis indicated that patients in the "2≤age<5" group and the "5≤age<16" group had very similar safety profiles. Forty-two (7.87%) patients in the "2≤age<5" group reported 58 AEs, of them, 44 were suspected to be treatment-related. Most of the AEs were mild and transient and only one patient experienced one SAE (rash). Skin and subcutaneous tissue disorders were the most frequently reported AEs (17 patients reporting 17 cases), followed by nervous system disorders in 14 patients (15 cases) and gastrointestinal disorders in 7 patients (11 cases). Meanwhile, 32 (7.39%) patients in the "5≤age<16" group reported 47 cases of AEs, of them, 30 cases experienced by 23 patients were suspected to be related to the treatment. Most of the AEs were mild and transient and no one experienced any SAE. Skin and subcutaneous tissue disorders were the most frequently reported (16 patients reporting 17 cases), followed by nervous system disorders in 9 patients (9 cases) and gastrointestinal

disorders in 6 patients (8 cases).

Laboratory examination revealed that 7 (0.72%) patients experienced asymptomatic hyponatraemia (Na^+ <135 mmol/L) during the study, none of them developed clinically significant hyponatraemia (Na^+ <125 mmol/L). Six (0.62%) and 16 (1.65%) patients have slightly elevated level of alanine aminotransferase and aspartate aminotransferase, respectively. No other clinically relevant abnormal laboratory parameters, abnormal EEG or physical examination results were detected.

Discussion

In this 26-week, multicenter, single-arm and observational study, we evaluated the efficacy and tolerability of OXC oral suspension in Chinese pediatric patients aged 2-16 years with PS or GTCS during routine clinical practice and found that OXC oral suspension treatment was effective in this group of patients regardless of their seizure types or gender and was well tolerated. Further, OXC treatment demonstrated similar efficacy and safety profiles in patients aged "≥2 years and <5 years" and "≥5 years and <16 years".

This study is similar to our other study on pediatric patients aged 2-5 years,[27] however, the age range of the eligible patients in the current study was extended and an age-based subgroup analysis ("2≤age<5 years" and "5≤age<16 years") was conducted to evaluate whether age impacted OXC treatment efficacy and tolerability. In addition, this study enrolled a larger population to gather more data. These two studies had very consistent results in terms of efficacy and safety.[27] The striking similarities between the efficacy and safety data of these two studies supported the validity of our proposal that OXC oral suspension was effective in treating pediatric patients with PS and/or GTCS and was well tolerated.

The age-based subgroup analysis revealed that OXC treatment had comparable efficacy and safety profiles in patients aged "≥2 and <5" and "≥5 and <16", implying that age might not play a role in OXC efficacy and safety. There has only been one study on whether a pediatric patient's age impacted OXC treatment and it found that OXC oral suspension had comparable efficacy and safety in infants (<1 year) and children (1-9 years).[18] Therefore, there is currently no solid evidence of age impacting the efficacy and safety of OXC treatment. More data are needed. However, at least for now, age shall not be a factor when a physician considers whether to prescribe OXC oral suspension to pediatric patients with PS and/or GTCS.

One of the efficacy measures used in this study was 100% seizure frequency reduction at the end of the 26-week treatment (0 seizure between week 26 and previous visit at week 13) as opposed to the seizure freedom during the entire trial commonly used in the previous studies.[2,16,19,20,24-26,29] 100% seizure frequency reduction at the end of the treatment allows for the possibility that a treatment might need time to demonstrate its efficacy for some patients and that lack of efficacy during the early phase of the treatment does not necessarily indicate poor efficacy later on. This efficacy measure still allows us to evaluate whether OXC treatment could lead to seizure freedom over an approximately 3-month period rather than the whole 6 to 36-month OXC treatment period used by other studies.[2,16,19,20,24-26,34] Such difference could account for the higher percentage of patients achieving 100% seizure frequency reduction (82.36%) at the end of the 26-week treatment in our study, as opposed to the 50%-69% achieving seizure freedom over the entire trial obtained by previous studies.[2,19,20,24-26]

Our current study and our another study on patients aged 2-5 years both showed that OXC oral suspension demonstrated good efficacy in all of the 4 seizure types (sPS, cPS, GTCS and PSSG) included in the studies. Results on whether seizure type impacts OXC treatment efficacy have been inconsistent.[15,16,18] Obviously, more in-depth studies on this topic are needed.

Our study also demonstrated that OXC treatment had comparable efficacies for male and female patients. Data on this topic are sparse, however our results were consistent with Yılmaz et al,[1] which reported that age did not play a role in determining whether the 289 pediatric patients taking phenobarbital, valproate, carbamazepine, oxcarbazepine, or levetiracetam became seizure free during a 12-month treatment period. However, since Yılmaz et al[1] included patients taking various different AEDs, more studies are needed to confirm our results.

We used retention rate in this study as an additional efficacy measure to evaluate the "effectiveness" of OXC treatment as recommended by International League Against Epilepsy.[35] The term "effectiveness" represents a composite measure of an AED's efficacy and tolerability associated with its long-term use and could be extremely helpful to physicians when they choose proper AED therapies for different patients. The retention rate of 92.4% obtained in this study suggested general effectiveness of OXC oral suspension for pediatric patients with partial PS and/or GTCS.

Our study demonstrated overall favorable safety profile associated with OXC oral suspension over the 26-week treatment period. 7.65% of the patients reported one or more AEs, and only one reported SAE

(rash). The most commonly reported AEs were rash (3.31%) followed by somnolence, myoclonus and fever, all of the reported AEs have been previously reported, with rash always being one of the most common types of AEs.[4,11,19,24] Prevalence of rash associated with OXC oral suspension in pediatric patients varied substantially from one study to another (0% to 16.7%), although reason(s) for such inconsistency are still unknown.[14,20,24,26] The rate of rash (3.31%) in our study is very close to the 3.2% obtained by Rufo-Campos et al.[20] Further, the fact that the rates of rash obtained by the current study and by our study on patients aged 2-5 years[27] were extremely close (3.31% *vs*. 2.97%) further supported the validity of our data. Patients in our study did not demonstrate known AEs associated with OXC such as dizziness, malaise and nystigamus,[4,11,17] the relatively short treatment duration of our study might be a contributing factor, on the other hand, patients of different ethnicities might demonstrate different types of AEs, of course, more studies are needed to explore this question.

There have always been concerns about OXC-associated hyponatraemia because OXC acts via modulating voltage-sensitive sodium and calcium channels.[7] Although it has been reported that hyponatraemia was more frequently associated with OXC treatment than carbamazepine in adult patients, most cases of OXC-associated hyponatraemia in pediatric patients were asymptomatic.[18] Seven patients in our study experienced asymptomatic hyponatraemia (Na^+ <135 mmol/L). The timing of its occurrence varied among different patients. Hyponatraemia was found in 3 patients at baseline, in 2 at week 4, in 1 at week 13 and in 1 at week 26. The patient who was found to have hyponatraemia at week 13 continued to have hyponatraemia at week 26. The fact that three patients already had hyponatraemia at baseline reduced number of patients suffering OXC-related hypornatraemia down to 4. For these hypornatraemic patients, daily monitoring of their blood sodium level was conducted until the blood sodium level returned to normal. None of these patients developed clinically significant hyponatraemia (Na^+ <125 mmol/L). This result was consistent with our study on patients aged 2-5 years[27] and was also consistent with a previous report.[18]

Also of note was the fact that our study did not exclude patients with rolandic seizure, the most common epileptic syndrome present in children.[36] As 20 patients presented with rolandic seizure were included in our study, some may be concerned that some patients with rolandic seizure might recover without treatment[36] and this could bias our result favorably. However, if remained untreated, it generally takes years for children with rolandic seizure to become seizure-free, often when they reach adolescence.[36,37] Our study was a 26-week study, a 26-week treatment period was too short for patients with rolandic seizure to recover spontaneously, and as such, we did not believe that our results on the efficacy of OXC could be affected by the fact that we included children with rolandic seizure in our study. In addition, OXC is one of the first-line medications for rolandic seizure,[37] therefore, treating these patients with OXC in our study was also suitable.

We chose weeks 4, 13 and 26 as our efficacy and safety assessment points because it is common to give OXC in a gradual dose titration to patients with seizure within one month according to OXC clinical protocol,[18] monitoring efficacy and safety at the end of this 1-month period was necessary since levels of OXC in the patients have not stabilized at this point. After completion of the dosage titration, weeks 13 and 26 represent the efficacy and safety profiles of the maintenance period, and are often used as assessment points for medium-term efficacy and safety of AEDs.[4]

One major limitation of our study is its relatively short duration, therefore long-term efficacy and safety profile beyond week 26 of OXC treatment couldn't be assessed in this study. In addition, our results showed a mean maintenance dose of 25.20±10.49 mg/kg/day (median: 24.62 mg/kg/day, range: 5.00-80.00 mg/kg/day), indicating that most patients took a dose close to 24.62 mg/kg/day and that our data distribution might not be very homogenous. We did not perform an age-based subgroup analysis on the mean maintenance dosage used for the "2≤age<5" and the "5≤age<16" subgroups, therefore we could not know whether the younger subgroup had a higher maintenance dose (mg/kg/day) *vs*. the older group, as suggested by prior reports and guidelines.[32] However, our analysis revealed no correlation between mean seizure frequency and mean maintenance dose at the end of the 26-week treatment (data not shown), suggesting that in the real-life setting, patients in our study received suitable dosage for their seizure as judged by their physicians, and as a result, we could make an age-based subgroup analysis on the efficacy of OXC as both groups of patients received suitable dose of OXC for their disease. On the other hand, the fact that our study was an observational study on OXC's efficacy and safety in real-life clinical practice has its strength, since it could assess real-life performance of OXC treatment in pediatric patients and thus could be conducive to generalization of its finding to routine clinical practice as it closely mirrored the real-world patient populations and treatment setting.

In conclusion, various clinical trials and studies conducted under controlled conditions have established the efficacy and safety of OXC treatment for pediatric

epilepsy; however, data on Chinese pediatric patients have been lacking. This study, by collecting, analyzing and reporting the real-world data, further confirmed the efficacy and good safety profile of OXC oral suspension in Chinese pediatric patients aged 2-16 years with PS or GTCS. It further suggested that age, gender or seizure types did not impact the efficacy and safety profile of OXC.

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