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Case Report

Efficacy and tolerability of perampanel in patients with genetic generalized epilepsy (GGE): A retrospective, single-center study from the United Arab Emirates (UAE)

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1. Introduction

Genetic generalized epilepsy (GGE) accounts for nearly a third of all epilepsy types, and perampanel has been approved by the US Food and Drug Administration (FDA) as an adjunctive treatment for primary generalized tonic–clonic seizures (PGTS) in patients >12 years and older in over forty countries worldwide [1,2]. Its efficacy and tolerability were evaluated in three phase III multi-centered, randomized, double-blind, placebo-controlled trials (Trials 304, 305, and 306) in patients with partial onset seizures (POS) despite receiving one to three AEDs [3,4,5,6]. Their findings demonstrated significant reduction in seizure frequency of partial-onset seizures, secondarily generalized seizures, and complex partial with secondarily generalized seizures, when compared with the placebo group (median percentage reduction from baseline per 28 days). Other clinical studies in real-life settings reported similar improvements in clinical outcomes [7]. While there are increasingly more trials being conducted in North America and Europe [8,9,10,11], this, to our knowledge, is the first retrospective study from the Middle East and North Africa (MENA) region, evaluating the use of perampanel as monotherapy and adjunctive treatment in the routine clinical care of patients with GGE.

2. Methods

The study was conducted at a private neurology clinic in Abu Dhabi, UAE and was approved by an internal Institutional Review Board at the American Center for Psychiatry and Neurology, in accordance with the International Conference on Harmonization-Good Clinical Practice (ICH-GCP). Twenty-one patients (females and males aged between 13 and 47), diagnosed with GGE according to the 2017 International League Against Epilepsy (ILAE) classification of epileptic seizures [12] and the 2017 ILAE classification of epilepsies and epileptic syndromes [13] were included in the study. They were included if they had a diagnosis of GGE during their clinical assessment by their attending neurologist (International Classification of Diseases, Tenth Revision, Clinical Modification) [ICD-10-CM code G40.309] and received perampanel as monotherapy or adjunctively with other AEDs between March 2018 and August 2018. Disposition chart of all 21 enrolled subjects included in the study is displayed in Fig. 1. All enrolled patients were started on PER treatment both as adjunctive and monotherapy between March 2016 and March 2018. Nineteen of the patients were taking an average of three AEDs prior to starting PER treatment, while the remaining two were put on PER monotherapy from the start of treatment.

Demographic and clinical data were collected from patients' clinical records upon obtaining their informed consent. These included age, sex, nationality, ethnicity, primary diagnosis, secondary diagnosis, previous AEDs, current concomitant AEDs, seizure type, seizure frequency, perampanel dose at titration, current perampanel dose, current perampanel treatment status, dose reduction, and reasons for dose reduction. We relied on patients' diaries to collect data on seizure frequency, checked at each clinic visit every four to six weeks; this is routinely scheduled for all patients with epilepsy. Adverse events were recorded on patients' medical archives at every clinic visit using open-ended questions. For dose titration, patients were initially put on a daily dose of 2 mg at night time, increased by 2 mg every two weeks until a 6 mg dose was maintained and well-tolerated. Further increments/decrements were made according to the neurologist's clinical judgment and based on patient response and tolerability. For safety assessments, treatment-emergent adverse events (TEAE), psychiatry-related adverse events, and reasons for discontinuation, if any, were recorded. Proportion of patients who were either previously or concomitantly on enzyme-inducing AEDs were also recorded. Tables 1 and 2 show patient demographics and epilepsy-specific details, respectively.

The primary efficacy endpoint was the percent decrease in seizure frequency. Seizure frequency was assessed by looking at the proportion of patients with a reduction in seizure frequency by at least 50%. The

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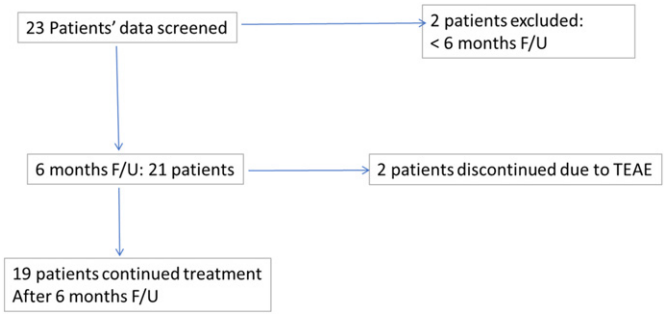

Fig. 1. Patient disposition of all 21 enrolled subjects at 6-month follow-up.

secondary efficacy endpoint was determined by the proportion of patients remaining on perampanel primary or conversion monotherapy at six months from baseline.

3. Results

There were 21 patients (12F, 9M), with a mean age of 27.48 years (13–47, SD ±9.72). The mean age of seizure onset was 12.19. Two patients started on perampanel as initial monotherapy and 19 others were on it as an add-on, with an average number of prior AED trials at 2.47 (1–5, SD 1.81). The average perampanel dose was 7.90. Two patients were excluded from the final analysis because follow-up was lost before reaching six months. Eight patients (38.1%) achieved a ≥50% reduction in seizure frequency at six months from baseline, while 11 patients (52.4%) achieved seizure freedom at the same interval of time. Nineteen patients (90.5%) remained on perampanel treatment beyond the six month follow-up from baseline, while two patients (9.5%) discontinued PER treatment due to treatment-induced adverse events; namely, dizziness and somnolence. Treatment-induced adverse events (see Table 3) were reported in 11 patients (52.4%), with the most common symptom being dizziness (4M, 2F). Out of those, nine patients (42.9%) continued treatment beyond six months. Five patients (23.8%) were reported as experiencing psychiatric-related adverse events (see Table 4), with irritability and depressive symptoms as the most common. However, none discontinued treatment. Four patients had comorbid diagnosis of major depressive disorder, but only two of them experienced psychiatric-related adverse events (irritability and worsening of depressive symptoms). Out of the four with psychiatric comorbidity, only one discontinued treatment but due to experiencing somnolence. Co-administered AEDs for these patients include Levetiracetam, Topiramate, Valproic Acid, Phenytoin, and Clonazepam. Three out of four were offered treatment for their psychiatric disorders but declined, while one was started on Escitalopram for the same. Three patients were concomitantly taking enzyme-inducing AEDs, namely, Topiramate, Phenytoin, and Phenobarbitone. One patient (taking Topiramate) discontinued treatment due to somnolence, and the other two experienced depressive symptoms but continued treatment. Seven patients (33.3%) were on perampanel monotherapy at the time of analyzing the current data, while the rest (57.1%) continued adjunctive treatment with the number of baseline AEDs reduced on average by 1.33 at the six month interval.

Table 1
Baseline patient demographics.

Demographics (full analysis set)	
N	21
Mean age, y (SD)	27.48 (9.72)
Female, n (%)	12 (57.1%)
Nationality/ethnicity, n (%)	
Emirati (Arab)	11 (52.4%)
Syrian (Arab)	3 (14.3%)
Sudanese (Arab)	2 (9.5%)
Egyptian (Arab)	1 (4.8%)
Yemeni (Arab)	1 (4.8%)
Palestinian (Arab)	1 (4.8%)
Omani (Arab)	1 (4.8%)
Indian (Asian)	1 (4.8%)
Age of onset, y (SD)	12.19 (7.16)

Table 2
Seizure-specific details.

Seizure-specific data	
Seizure type, n (%)	
Tonic–clonic	21 (100%)
Myoclonic	16 (76.2%)
Absence	2 (9.5%)
Atonic	1 (4.3%)
Number of previous AED trials (discontinued prior to starting PER)	14 (66.7%)
1	6 (28.6%)
2	5 (23.8%)
3	5 (23.8%)
4	1 (4.8%)
5	2 (9.5%)
Reasons for previous AED(s) discontinuation	
Inadequate efficacy	10 (47.6%)
Poor tolerability	4 (19.1%)
Number of concomitant baseline AEDs	17 (80.9%)
1	6 (26.6%)
2	8 (38.1%)
3	3 (14.3%)
Patients on concomitant enzyme-inducing AEDs	3 (14.3%)
Patients who had dose reduction due to TEAE	3 (14.3%)
Reasons for dose reduction	
Dizziness	1 (4.8%)
Agitation	1 (4.8%)
Aggression	1 (4.8%)
Increased hand tremors	1 (4.8%)
Patients currently on perampanel monotherapy	7 (33.3%)
Current AEDs	
Perampanel monotherapy	7 (33.3%)
Adjunctive perampanel	12 (57.1%)
Others (discontinued perampanel)	2 (9.52%)
Patients who had ≥50% response rate	19 (90.5%)
Patients who achieved seizure freedom	11 (52.4%)

4. Discussion

This retrospective study evaluated archives of clinical data on 21 patients with genetic generalized epilepsy who received perampanel treatment as both monotherapy and adjunctive therapy. We evaluated the efficacy and tolerability of perampanel with a minimum of six month follow-up and observed a 38.1% seizure reduction and 52.4% seizure freedom rate in our cohort. There was also a 90.5% response rate where patients continued treatment beyond six months from baseline. On average, the 19 patients who continued with adjunctive treatment had 1.33 of their baseline AEDs discontinued with the prospect of achieving perampanel monotherapy. Comparing the results to the three phase-III randomized regulatory trials which evaluated perampanel treatment for partial seizures (studies 304, 305, and 306), seizure reduction rates at 8 mg/day dose ranged between 33.3% and 37.6%, similar to the observed 38% responder rate in this cohort [3,4,5]. However, their seizure freedom rate was much lower and ranged between 2.2% and 4.8% at a dose of 8 mg/day.

The most common TEAE among our cohort was dizziness, causing one out of the six patients with the experience to discontinue treatment. The three regulatory trials also reported dizziness, irritability, and aggression as the most common adverse effects causing at least 1% of their studied population to discontinue treatment [3,4,5]. A retrospective multicenter study [7] from Spain also found dizziness as the most common TEAE in their studied cohort. Moreover, a sub analysis of the phase III trials which looked at perampanel efficacy and safety by gender found female subjects experienced dizziness and headache more frequently than males [11]. In our cohort, four out of the six patients who experienced dizziness were female among whom one patient

Table 3
Treatment-emergent adverse events (TEAE).

TEAE	N (%)	Onset of TEAE	Relation to dose escalation	Action taken	Outcome at last FU
Dizziness	6 (28.6%)	Between week 2 and week 4	Probably related	No action taken (3 cases)	Resolved
				Dose reduced (2 cases)	Resolved
				Drug withdrawn (1 case)	Resolved
Somnolence	1 (4.8%)	Week 4	Probably related	Drug withdrawn	Resolved
Headache	1 (4.8%)	Between week 4 and week 6	Probably related	No action taken	Resolved
Blurred vision	1 (4.8%)	Week 8	Possibly related	No action taken	Resolved
Decreased libido	1 (4.8%)	Week 8	Possibly related	No action taken	Resolved (improved over several weeks of follow-up)
Weight gain	1 (4.8%)	Week 8	Probably related	No action taken	Resolved (improved over several weeks of FU)
Snoring	1 (4.8%)	Week 8	Possibly related	No action taken	Resolved (improved over several weeks of FU)
Diarrhea	1 (4.8%)	Between week 4 and week 6	Possibly related	No action taken	Resolved (improved over several weeks of FU)
Depressive symptoms	3 (14.3%)	Week 4	Probably related	No action taken	Resolved
Irritability	2 (9.5%)	Week 4	Probably related	No action taken	Resolved
Anxiety	1 (4.8%)	Week 4	Probably related	No action taken	Resolved
Agitation	1 (4.8%)	Week 6	Probably related	Dose reduced	Resolved
Aggression	1 (4.8%)	Week 6	Probably related	Dose reduced	Resolved

also experienced headache. Our study also found five patients (23.8%) having had experienced psychiatry-related adverse events. Irritability and depressive symptoms were the most common, although none of the reported patients discontinued treatment because of them. Safety data from the three phase-III trials show that irritability and aggression were dose-related occurrences although the investigators did not confirm causality [14]. It is important to mention that four of the patients in our cohort had pre-existing psychiatric diagnoses and two of them reported worsening of their symptoms, which could be a predicting factor of the PRAE associated with perampanel treatment.

Other real-world studies such as the one by Villanueva and colleagues [15] have reported similar results while also looking at different seizure types in GGE. Juvenile myoclonic epilepsy (JME) was the most common syndrome in their subjects at 40%, compared with 76% in the current cohort. The seizure-freedom rate was similar at 59% across all seizure types compared with 52.4% in the current study. Fifty percent of the patients with JME in the current cohort achieved seizure freedom whereas their study reported 65% among the same group. This study [15] also reported dizziness as one of the most common treatment-emergent adverse events. Relatedly, a randomized, multicenter, double-blind study [8] on patients with tonic–clonic seizures in GGE

Table 4
Clinical characteristics related to PER.

Exposure to adjunctive therapy	Syndrome classification[a]	Type of seizures	Seizure frequency before PER	Seizure frequency after PER
Yes	GTCA	Tonic–clonic	Once every eight weeks	Zero
Yes	JME	Tonic–clonic	Once every two months	
		Myoclonic	Three times per week	Zero
Yes	JME	Tonic–clonic	Once per month	
		Myoclonic	Once per week	Zero
Yes	JME	Myoclonic	Four times daily	Zero
Yes	JME	Tonic–clonic	Twice per week	Once per week
		Myoclonic	Four times daily	Once per day
		Absence	Once daily	Once every three weeks
		Atonic	Once per week	Once per month
Yes	JME	Tonic–clonic	Once every three months	Zero
		Myoclonic	Four times per day	Once per day
Yes	JME	Myoclonic	Twice per day	Once every two weeks
No	JME	Tonic–clonic	Once per month	Zero
Yes	JME	Myoclonic	Four times per day	Zero
Yes	JME	Tonic–clonic	Once per month	Zero
		Myoclonic	Two–three times per day	Zero
No	JME	Tonic–clonic	Once every two months	Zero
		Myoclonic	Three times per week	Zero
Yes	JME	Tonic–clonic	Three–four per week	Once per week
		Myoclonic	Three–four per day	Twice per week
Yes	JME	Tonic–clonic	Once per week	Once every two months
		Myoclonic	Three times per week	Once every two weeks
Yes	JME	Tonic–clonic	Once every two weeks	Once every six–eight weeks
		Myoclonic	Once daily	Once every seven–ten days
Yes	JME	Tonic–clonic	Once every three–four months	Zero
		Myoclonic	Two–three times per week	Zero
Yes	JAE	Tonic–clonic	Once per week	Zero
		Absence	Once daily	Zero
Yes	GTCA	Tonic–clonic	Once per month	Once every two–three months
Yes	GTCA	Tonic–clonic	Twice per month	Once every two–three months
Yes	JME	Tonic–clonic	Once per month	
		Myoclonic	Once or twice per week	Discontinued due to AE
Yes	JTCA	Tonic–clonic	Twice per month	Zero
Yes	JME	Tonic–clonic	Two–three times per month	
		Myoclonic	Three–four times per week	Discontinued due to AE

[a] GTCA — generalized tonic–clonic seizures alone; JME — juvenile myoclonic epilepsy; JAE — juvenile absence epilepsy.

had a comparable rate of seizure freedom at 30.9%. Moreover, the same study had enrolled subjects who were also using between one and three AEDs, and reported dizziness as one of the most common treatment-emergent adverse events. The percentage of patients with generalized tonic–clonic seizure type (81%) receiving perampanel treatment was comparable to the current cohort (86%). Unlike the current cohort, however, this study [8] had 11.1% of patients discontinuing treatment due to psychiatric-related adverse events, including severe cases of abnormal behavior, aggression, anxiety and insomnia, mood swings, suicidal ideation and suicide attempt. That said, in the current cohort, a 23-year-old male patient who experienced behavioral issues (agitation and aggression) had his dose temporarily reduced to 4 mg from 6 mg/day. Some studies have reported higher rates of occurrence in psychiatric-related adverse events when administering perampanel as compared with any other antiepileptic drugs [16,17]. The occurrence of both treatment-emergent and psychiatric-related adverse events suggests that patients should be monitored carefully for clinical response and tolerability, and dosing should be individualized as part of the routine clinical care. None of the patients in this cohort reported experiencing suicidal or homicidal ideation threats.

This study has some limitations: the sample, while being small, is also made up of a heterogeneous group and data was collected retrospectively, potentially creating selection bias of results. It would have also been preferred if archived data beyond six months was considered to draw more meaningful conclusions. Abu Dhabi being one of the most developed cities in the Middle East and North Africa (MENA), generalizability of the results to other less affluent areas in the region is restricted where quality of life, access to, and quality of treatment may be limited. Nevertheless, we anticipate that it provides additional insight into the use of perampanel as both monotherapy and adjunctive treatment for GGE.

5. Conclusion

Our study provides supplemental information towards the decision to approve perampanel as monotherapy, based on similar findings from retrospective and non-interventional studies in various locations in Europe and Russia [7,15]. Our findings, although based on a relatively smaller sample size, are representative of a population from the Middle East and North Africa region and suggest that perampanel is well-tolerated in patients with GGE. For non-compliant patients, monotherapy may ease the burden of having to take multiple AEDs daily, but slow-titration is always preferred to lessen the occurrence of TEAEs including PRAEs.

Ethical statement

The study was approved by an internal Institutional Review Board at the American Center for Psychiatry and Neurology, in accordance with the International Conference on Harmonization-Good Clinical Practice (ICH-GCP). Informed consent was solicited from patients after explaining the voluntary nature of the study and guaranteeing confidentiality and anonymity.

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Declaration of competing interest

The authors declare they have no competing interests regarding the publication of this paper.

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