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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A R T I C L E   I N F O

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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 United States 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 multicenter, randomized, double-blind, placebo-controlled trials (Trials 304, 305, and 306) in patients with partial onset seizures (POS) despite receiving one to three antiseizure drugs (ASDs) [3–6]. These findings demonstrated significant reduction in seizure frequency of focal partial-onset seizures including focal impaired awareness seizures and focal to bilateral tonic-clonic seizures when compared with a 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 clinical trials being conducted in North America and Europe [8–11], 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 IGE.

2. Methods

The study was conducted at a private neurology clinic in Abu Dhabi, United Arab Emirates (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 (f.k.a. Idiopathic Generalized epilepsy) during their clinical assessment by their attending neurologist (International Classification of Diseases, Tenth Revision, Clinical Modification) [ICD-10-CM code G40.xxx] and received perampanel as monotherapy or adjunctively with other ASDs between March 2018 and August 2018. Disposition charts 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 ASDs prior to starting PER treatment, while the remaining two were begun 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, gender, nationality, ethnicity, primary diagnosis, secondary diagnosis, previous ASDs, current concomitant ASDs, 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. This was checked at each clinic visit every four to six weeks and is routinely scheduled for all patients with epilepsy. Adverse events were recorded on patients’ medical records at every clinic visit using open-ended questions. For dose titration, patients were initially placed on a daily dose of 2 mg at night time and 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 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 (12 females), with a mean age of 27.48 years (range: 13–47, SD ± 9.72). The mean age of seizure onset was 12.19 years old. Two patients started on perampanel as initial monotherapy, and 19 others were on it as an add-on, with an average number of prior ASD 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. Eleven patients (52.4%) achieved a ≥50% reduction in seizure frequency at six months from baseline, while eight patients (38.1%) 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 a comorbid diagnosis of major depressive disorder, and two of them experienced psychiatric-related adverse events (irritability and worsening of depressive symptoms). Out of the four with psychiatric comorbidity, one discontinued treatment due to somnolence. Coadministered ASDs 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 ASDs, namely, topiramate, phenytoin, and phenobarbital. One patient (taking topiramate) discontinued treatment due to somnolence, and the other two experienced depressive symptoms but continued.

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 (%)    |   | 11 (52.4%) |
| 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 ASD Trials (discontinued prior to starting PER) |
| 1                      | 6 (28.6%) |
| 2                      | 5 (23.8%) |
| 3                      | 5 (23.8%) |
| 4                      | 1 (4.8%) |
| 5                      | 2 (9.5%) |
| Reasons for previous ASD(s) discontinuation |
| Inadequate efficacy    | 10 (47.6%) |
| Poor tolerability      | 4 (19.1%) |
| Number of Concomitant baseline ASDs |
| 1                      | 6 (28.6%) |
| 2                      | 8 (38.1%) |
| 3                      | 3 (14.3%) |
| Patients on concomitant enzyme-inducing ASDs |
| 1                      | 3 (14.3%) |
| Patients who had dose reduction due to TEAE |
| 1                      | 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 |
| 1                      | 7 (33.3%) |
| Current ASDs |
| Perampanel monotherapy  | 7 (33.3%) |
| Adjunctive Perampanel  | 12 (57.1%) |
| Others (discontinued Perampanel) |
| 1                      | 2 (9.5%) |
| Patients who had ≥50% response rate |
| 1                      | 19 (90.5%) |
| Patients who achieved seizure freedom |
| 1                      | 11 (52.4%) |
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 months interval.

4. Discussion

This retrospective study evaluated the medical records of 21 patients with GGE 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.

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 [3–5]. 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 also experienced headache. Our study also found five patients (23.8%) having had experienced psychiatry-related adverse events.

Table 3
Treatment-emergent adverse events in patients treated with perampanel.

| 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           |
| Somnolence            | 1 (4.8%) | Week 4        | Probably related | Drug reduced (2 cases)     | 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 (improved over several weeks of follow up) | Resolved |
| 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 (improved over several weeks of FU) | Resolved |
| 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 6        | Probably related | No action taken (improved over several weeks of FU) | Resolved |
| Agitation             | 1 (4.8%) | Week 6        | Probably related | Dose reduced               | Resolved           |
| Aggression            | 1 (4.8%) | Week 6        | Probably related | Dose reduced (improved over several weeks of FU) | Resolved |

8 mg/day dose ranged between 33.3% and 37.6%, similar to the observed 38% responder rate in this cohort [3–5]. 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 four 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 [3–5]. 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 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

Table 4
Clinical characteristics related to perampanel.

| Exposure to adjunctive therapy | Syndrome classification | Type of seizures | Seizure frequency before PER | Seizure frequency after PER |
|--------------------------------|-------------------------|------------------|-----------------------------|-----------------------------|
| Yes                            | GTCA                    | Tonic–clonic     | Once every eight weeks      | Zero                        |
| Yes                            | JME                     | Tonic–clonic Myoclonic | Once every two months Three times per week | Zero                        |
| Yes                            | JME                     | Tonic–clonic Myoclonic | Once per month | Once per week | Zero                        |
| Yes                            | JME                     | Tonic–clonic      | Four times daily | Zero | Zero                        |
| Yes                            | JME                     | Tonic–clonic Myoclonic | Twice per week Four times daily | Once per week | Zero | Once per day |
| Yes                            | JME                     | Tonic–clonic Myoclonic | Once per three months Four times per day | Zero | Once per day |
| Yes                            | JME                     | Tonic–clonic Myoclonic | Four times per day | Zero | Zero                        |
| Yes                            | JME                     | Tonic–clonic Myoclonic | Once per month two-three times per day | Zero | Zero | Zero |
| Yes                            | JME                     | Tonic–clonic Myoclonic | Three-four per week Three-four per day | Once per week | Zero | Zero |
| Yes                            | JME                     | Tonic–clonic Myoclonic | Once per two weeks | Once per six-eight weeks | Zero | Zero |
| Yes                            | JME                     | Tonic–clonic Myoclonic | Once every three-four months Two-three times per week | Zero | Zero |
| Yes                            | JAE                     | Tonic–clonic Absence | Once per week | Once per day | Zero | Zero |
| Yes                            | GTCA                    | Tonic–clonic     | Once per month | Zero | Zero |
| Yes                            | JME                     | Tonic–clonic     | Twice per month | Once every two-three months | Zero | Zero |
| Yes                            | JME                     | Tonic–clonic Myoclonic | Once per month | Once every two-three months | Discontinued due to AE |
| Yes                            | JAE                     | Tonic–clonic     | Twice per month | Discontinued due to AE |

a GTCA – Generalized tonic–clonic seizures alone; JME – Juvenile Myoclonic Epilepsy; JAE – Juvenile Absence Epilepsy
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 half of them reported worsening of their symptoms, which could be a predictive factor of the psychiatric-related adverse effects 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 to 76% in the current cohort. The seizure-free rate was similar at 59% across all seizure types compared to 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. Similarly, a randomized, multicenter, double-blind study [8] on patients with tonic–clonic seizures in GGE 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 ASDs, 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 and successfully reduced to 4 mg/day from 6 mg/day. Some studies have reported higher rates of occurrence in psychiatric-related adverse events when administering perampanel as compared to any other antiseizure drugs [16,17]. The occurrence of both treatment-emergent and psychiatric-related adverse events suggest 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 is small and is made up of a heterogeneous group of patients with GGE. In addition, the data was collected retrospectively, potentially creating a selection bias of the retrospective and non-interventional studies performed in other 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.

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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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[14] Ettinger AB, LoPresti A, Yang H, et al. Psychiatric and behavioral adverse events in perampanel as monotherapy in the Middle East similar to other reports from retrospective and non-interventional studies performed in other 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.

**5. Conclusion**

Our study provides adds to information on the utility and effectiveness of perampanel as monotherapy in the Middle East similar to