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Efficacy and tolerability of treatment with lacosamide: Postmarketing experience from the Middle East region

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ABSTRACT

Purpose: Lacosamide (LCM) was recently introduced in the Middle East. The aim of this study was to evaluate the safety, tolerability, and efficacy of LCM in patients with focal onset seizures and determine if our results are comparable with those derived from Western countries.
Methods: This is a retrospective analysis from two medical centers on consecutive patients diagnosed as having focal onset seizures and treated with add-on LCM. The primary efficacy variables were the 50% responder and seizure-free rates, and the secondary outcome variables included the percentages of patients who achieved seizure remission during the last 6-month follow-up period and the percentages of discontinuation due to lack of efficacy or tolerability.
Results: One hundred four patients with a mean age of 30.9 years and experiencing a mean of 9.4 seizures per month during baseline were included. The 50% responder rates were 69% and 70% at 6- and 24-month follow-ups, respectively. Patients concomitantly treated with a sodium channel blocker were less likely to achieve seizure remission during the last 6-month follow-up period while the early introduction of LCM resulted in a significantly higher likelihood of achieving such a remission. Eighty-eight percent of patients were still maintained on LCM at the last follow-up, and the most common adverse events consisted of dizziness and somnolence, double vision, and nausea/vomiting.
Conclusions: Our data show similar efficacy and tolerability to those reported from Western countries. Our results also substantiate the early introduction of LCM and support the dose reduction of baseline AED especially that of sodium channel blockers to minimize adverse events.

1. Introduction

Lacosamide (LCM) is one of the latest antiepileptic drugs (AEDs) that was recently introduced in the Middle East region and initially approved as adjunctive therapy in adults with focal onset seizures. It was also recently approved by the FDA as monotherapy for adults with focal onset seizures based on a superiority trial compared with historical controls [1] and by the EMEA based on a comparative noninferiority trial versus carbamazepine (CBZ) controlled release (CR) [2].

Lacosamide is believed to have a novel mechanism of action and exert its anticonvulsant effect by selective enhancement of the slow inactivated sodium channels. It is also characterized by a favorable pharmacokinetic profile with low protein binding and a virtual lack of drug–drug interactions and by good efficacy and tolerability as documented in the pivotal add-on clinical trials [3].

The open label studies describing the postmarketing experience with LCM have provided additional information on its efficacy and tolerability in cohorts that are more representative of the patient population encountered in daily clinical practice [4–8]. All those studies were conducted in Europe or the United States with no available published data on the clinical experience with LCM from Arab countries. This study was designed to evaluate the safety, tolerability, and efficacy of adjunctive treatment with LCM in patients with refractory focal onset seizures evaluated at two tertiary medical centers to determine if our results are in line with those derived from Western countries.

2. Materials and methods

2.1. Study design and participants

This was a retrospective analysis from two medical centers on consecutive patients diagnosed as having uncontrolled focal onset seizures treated with add-on LCM in addition to their baseline AED regimen between 2013 and 2015. The inclusion criteria included patients

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experiencing complex focal and/or secondarily generalized tonic–clonic seizures (GTCs) and who were treated with add-on LCM. Patients who only experienced simple focal seizures with subjective symptoms were excluded.

At each visit, the type and number of seizures were tabulated. Patients were queried about the presence of adverse events by asking an open ended question: "Are you experiencing any adverse events?". The presence, type, and severity of adverse events considered to be related to LCM by the investigators were included in the analysis. For patients who decided to discontinue LCM, the cause of discontinuation (lack of efficacy or tolerability) was documented.

We extracted from chart review a number of variables including patient demographics, seizure type and electroclinical syndrome, age at seizure onset and duration of epilepsy, previous AEDs tried, number and types of AEDs at baseline, and monthly baseline seizure frequency for the three months prior to starting treatment with add-on LCM. We also reviewed the brain MRIs for the presence or absence of an epileptogenic lesion on neuroimaging. Baseline AEDs were stratified into sodium channel blockers (phenytoin, CBZ, oxcarbazepine (OXC), eslicarbazepine, and lamotrigine (LTG)) or nonsodium channel blockers (all other AEDs). In addition, we obtained the daily dose of LCM and seizure frequency (based on seizure diaries) at every 3-month intervals. The study was approved by the institutional review boards of the two medical centers.

2.2. Statistical analysis

The change in seizure frequency after the introduction of LCM was compared with the three-month baseline seizure frequency. The primary efficacy variables were the 50% responder rate and seizure-free rates, and the secondary outcome variables included the percentages of patients who achieved a seizure remission during the last 6-month follow-up period and the percentages of discontinuation due to lack of efficacy or tolerability. The 50% responder and seizure-free rates were calculated every 3 months based on the seizure diaries obtained at each follow-up visit. We also correlated the efficacy of LCM according to its order of administration and stratified its efficacy according to whether it was added to a regimen that included a sodium channel blocker or not.

For continuous variables, descriptive statistics including mean, median, range, and frequencies with percentages were calculated.

Statistical analysis was performed using chi-square test or Fisher exact test for categorical variables. Significant P values were set at <0.05.

3. Results

3.1. Demographics

Out of the 116 patients treated with LCM, 12 patients were excluded for not fulfilling the inclusion criteria (3 patients experienced seizure types that included absence or atypical absence seizures, two were diagnosed as having primarily GTCs, three experienced tonic seizures, and four patients experienced only simple partial seizures with subjective symptoms). Therefore, a total of 104 patients (71 patients from center 1 and 33 patients from center 2) were analyzed.

There were 47 men (45%) and 57 women (55%), with a mean age of 30.9 years (range: 12–65 years). The mean age at seizure onset was 14.8 years (range: 1 month–63 years), and the mean baseline monthly seizure frequency was 9.4 (range: 0.25–60; median: 5 seizures). Ninety-one patients (88%) experienced complex partial seizures and averaged 7.6 seizures per month while 34 patients (33%) experienced secondarily GTCs with an average of 1.8 seizures per month. The mean length of follow-up was 13.6 months (range: 2–34 months), and the mean daily maintenance dose of LCM was 329 mg (range: 100–600 mg/day). At baseline, 33 patients (32%) were on one AED, 37 (36%) were on two AEDs, 23 (22%) were on three AEDs, and 9 (9%) were on four AEDs. Seizures in the remaining two patients had previously failed to improve with one and four AEDs, respectively. At their initial visit, they were not maintained on any anticonvulsant, and it was decided to treat them with LCM as monotherapy. The most common baseline AEDs were levetiracetam used by 63% of patients, followed by OXC in 27%, LTG in 25%, CBZ in 23%, and valproate in 20%. Sixty-five patients (63%) were maintained on a sodium channel modulator (CBZ, OXC, or LTG) at baseline.

The typical titration schedule of LCM consisted of an initial dosage of 100 mg/day administered twice daily with weekly increment of 100 mg daily until a daily LCM dose of 300 mg was reached. Further increment in the LCM dosage up to 600 mg/day was based on the clinical response. For patients maintained on a sodium channel modulator at baseline, the daily dose of that AED was reduced by approximately 20% at the time of initiating add-on treatment with LCM.

3.2. Patient disposition

Of the 104 patients included in this study, 92 patients (88%) were still on LCM at the last follow-up visit. Those patients were maintained on a mean daily LCM dose of 331 mg (range: 100–600 mg) and were followed for a mean duration of 14.6 months (range: 6–34 months). Of the 12 patients (12%) who discontinued LCM, 9 did so because of lack of efficacy, two because of adverse events, and one because of lack of efficacy and adverse events. Seven of the nine (78%) patients who discontinued because of lack of efficacy were on a concomitant sodium channel modulator and were maintained on a mean LCM dose of 333 mg. There was no significant difference in the mean daily dose of LCM between those who prematurely discontinued because of lack of efficacy (340 mg) and those who did not (331 mg).

3.3. Efficacy

The 50% responder rates ranged between 65% and 74% at various lengths of follow-up with no evidence for the development of tolerance over a period of 24 months (Fig. 1). The seizure-free rates for patients exposed to LCM for up to two years ranged between 23% and 26% (Fig. 1). The percentage of patients who experienced more than 50% worsening in their seizure frequency compared with baseline ranged between 1% and 8% (Fig. 1).

The median reduction in seizure frequency for complex partial seizure (CPS) as compared with baseline was maintained throughout the 24 months follow-up period and ranged between 87% and 88%. Similarly, the median reduction for both CPS and secondarily GTC ranged between 85.0% and 88.2%. The median reduction in secondarily GTC at all follow-up periods was 100% (Fig. 2).

Of the 104 patients enrolled in this study, 28 (27%) achieved seizure remission during the last 6-month follow-up period on a mean daily dose of 321 mg. Patients who discontinued LCM because of lack of efficacy or adverse events were included in the group with persistent seizures.

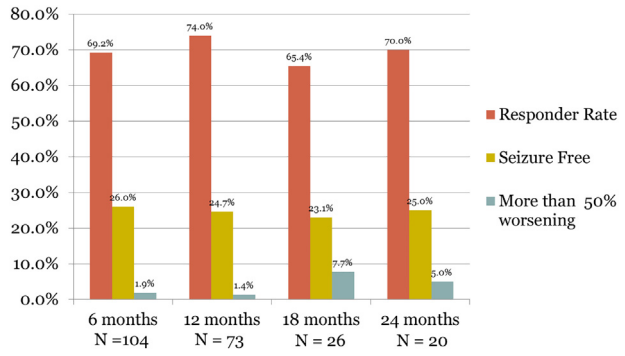

Fig. 1. Fifty percent responder rates, seizure-free rates, and percentages of patients with more than 50% worsening in seizure frequency at various lengths of follow-up.