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Clinical outcomes of perampanel vs. lacosamide in cohorts of consecutive patients with severely refractory epilepsies — A monocentric retrospective analysis of systematically collected data from the German Kork Epilepsy Center

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ABSTRACT

Purpose: Perampanel (PER) and lacosamide (LCM) are antiepileptic drugs (AEDs) approved for the adjunctive treatment of partial-onset seizures. At the time of market entry, information on clinical effectiveness of new AEDs is limited to results from pivotal trials, real-life or comparative data are missing. This analysis of data collected retrospectively in a German epilepsy center used unified evaluation criteria, and describes treatment outcomes with LCM and PER at 6 months.
Methods: Results of the first 70 consecutive patients who had received LCM or PER after their market entries in Germany were compared. Outcome measures comprised 50% responder rates, seizure freedom, retention, and incidence of adverse events (AEs).
Results: The mean number of previous AEDs was 8.7 in the PER group, and 7.3 in the LCM group. At 6 months, the 50% responder rate for all seizures was 48.6% for PER, and 28.6% for LCM, with seizure freedom in 14.3% of patients with PER, and 4.3% with LCM. Thirty-two AEs were reported for LCM, and 51 for PER, most commonly *dizziness* (22.9% of patients) for LCM, and *somnolence/tiredness* for PER (41.4%). AEs were reported as primary reason for discontinuation in 3 patients of the PER group. Retention rates were similar.
Conclusions: This analysis describes initial comparative benefits of two newly available AEDs in two cohorts of patients with highly refractory epilepsies. Responder and seizure freedom rates were numerically higher for PER. The analysis suggests that new AEDs can provide a chance for seizure freedom in relevant subgroups of patients, despite previous failure of multiple AEDs.

1. Introduction

Antiepileptic drugs (AEDs) newly licensed for use as adjunctive therapy are usually reserved to treat patients with severely refractory epilepsies in specialized epilepsy centers, presenting with long-standing illness and multiple previous drug failures.

Information regarding efficacy, tolerability and safety for an AED at this stage mainly originates from randomized controlled trials (RCTs) designed to evaluate the efficacy of the drug compared to placebo, and to serve as basis to assess a drug's overall benefit–risk ratio in the regulatory context. The external validity of RCTs may be limited by factors like relatively short trial durations, the usage of fixed dose regimens with stable baseline medication, and rapid dose escalations [1].

With regard to the even more complex question of comparative efficacy and tolerability, recent systematic reviews and meta-analyses indicate that comparisons of newer AEDs based on RCT data fail to consistently identify differences in efficacy and other outcome measures on a larger scale due to methodologic issues or the small magnitude of any difference in effect [2–4]. Consequently, pivotal trial data in the adjunctive setting appear to be of limited value for evaluating the utility of AEDs in routine practice and differentiating between drugs in this context. In addition, heterogeneity in, and lack of complete information regarding baseline conditions and patient refractoriness across AED registration trials conducted over the past twenty years [5] may further

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complicate conclusions regarding comparative AED outcomes, leaving the clinician widely uninformed regarding optimal drug choice for individual patients.

Against this background, the collection, evaluation, and timely communication of first post-marketing experiences with new AEDs in tertiary epilepsy centers, especially in traditional "early launch" countries like Germany, can be relevant early sources of information for physicians in Europe and other parts of the world, delivering valuable insights into a new drug's real-life benefit and providing relevant recommendations on, for example, approaches to clinical use beyond information contained in a drug's prescribing information [6,7]. Still, comparative data based on real-life observations is scarce, as first-experience reports naturally focus on observations for single drugs after their respective market entries. Unless based on a uniform assessment protocol, post-hoc analyses of data collected across different centers appear to be of limited informative value in this respect due to variable depth of information, differences in observational periods, heterogeneous or undisclosed information regarding baseline conditions, or differing evaluation criteria.

For two of the newer AEDs, lacosamide (LCM), a novel sodium channel blocker approved for the adjunctive treatment of partial-onset seizures (POS) with or without secondary generalization in patients aged 16 years and older in 2008, and perampanel (PER), a novel, selective non-competitive AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid)-type glutamate receptor antagonist approved for the adjunctive treatment of POS with or without secondary generalization in patients aged 12 years and older in 2012, and for the adjunctive treatment of primary generalized tonic-clonic seizures in patients with Idiopathic Generalized Epilepsy aged 12 years and older in 2015, first clinical experiences from the German tertiary Kork Epilepsy Center had been collected and published independently in 2012 (for LCM, Ref. [8]) and 2014 (for PER, Ref. [9]). Although both publications described favorable results for PER and LCM in groups of patients with difficult-to-treat epilepsies, comparability of the reported outcomes are impeded by a significant difference in the length of the reported follow-up period (6 months for PER vs. 12 months for LCM), some ambiguity regarding the operationalization of seizure outcomes, and incomplete or missing information regarding potentially influential factors like seizure situation at baseline, or detailed information regarding concomitant and previously failed AEDs. Particularly the latter aspect is of special interest, as it was shown that the efficacy of a newly introduced AED and the associated chance of seizure freedom appears to be strongly predetermined by the number of previously failed AEDs [10].

To facilitate the comparability of first experiences for PER and LCM collected in the Kork Epilepsy Center in two cohorts comprising consecutive patients, who first had received these new AEDs after their introduction in Germany, and to further elucidate AED treatment and pre-treatment status of both cohorts at baseline, a retrospective analysis based on chart review of individual patients along predefined variables and with unified evaluation criteria was conducted, the results of which are reported in this manuscript.

2. Methods

2.1. Design, inclusion criteria, rationale for choice of cut-off date, and patient management

This was a retrospective single center data collection based on individual chart review with subsequent analysis of baseline demographic and epilepsy-related characteristics, and measures of AED efficacy, tolerability, and retention. Outcomes of the first 70 consecutive patients who had started PER in the Kork Epilepsy Center between September and December 2012, for whom follow-up data for a minimum of 6 months was available, were evaluated, and results were contrasted with the outcomes of the first 70 consecutive patients treated with LCM who had started the drug in September 2008. A 6 month data cut-off was defined, ending for PER in June 2013.

This cut-off date was chosen to avoid potential influences of factors beyond clinical considerations, especially related to future disparate drug accessibility, as it was announced at the end of June 2013, that PER would be withdrawn from the German market. This followed the ruling of the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA), the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany, that no evidence of an additional benefit of PER over comparative therapies had been provided. The G-BA commented that the presented clinical studies were not appropriate to assess the additional benefit, as the G-BA-defined comparative therapy had not been implemented. The decision was based on new legislation aimed at regulating the German drug market, effective from 2011 only, thus impacting PER, but not LCM.

Follow-up frequency was consistent with routine clinical practice and was usually between three and six months. At each follow-up visit, seizure details (based on seizure logs maintained by the patient), side effects, and complications since the last visit were retrieved. Clinical management of patients was performed by BJS and CK. Dosage of anticonvulsive co-medication was kept stable during the time patients received LCM or PER. Both drugs were dosed based on individual seizure frequency/severity and tolerability.

2.2. Parameters and data entry

An observational plan was prepared beforehand, detailing scope of the analysis, methods and operationalization of outcome measures. Variables to be assessed were defined in accordance with the observational plan, and prior to data collection. Chart review and data entry was performed by an experienced epileptologist (CK) by means of a standardized evaluation sheet in Excel.

The following baseline data was collected: gender, age, etiology (structural/metabolic; unknown; other), time since diagnosis (in years), seizure frequency for simple partial seizures, complex partial seizures, secondarily generalized seizures, and total seizure count (per month) before the introduction of PER or LCM into the therapeutic regimen, respectively. Furthermore, all concomitant and previous AEDs were to be specified; the Excel sheet comprised a list of 21 specific AEDs plus an "other" category, for which information on a "current" or "previous" use was to be derived from available patient charts.

The following outcome variables were to be completed: Response (defined as a minimum of 50% reduction in seizure frequency vs. baseline; yes/no), for all seizure types, and for secondarily generalized tonic-clonic (SGTC) seizures, as far as sufficient information was available for the latter; seizure freedom (for a minimum of 3 months prior to the cut-off date; yes/no), for all seizure types, and for SGTC seizures, as far as sufficient information was available for the latter; drug retention at 6 months (yes/no); if not retained, primary reason for discontinuation [adverse event (AE); insufficient efficacy, other]; if not retained: duration of treatment with PER or LCM, respectively (in weeks). For the evaluation of AEs within the evaluation period of 6 months, a list of 8 AE qualities was compiled based on AEs reported in the PER and LCM publications [8,9], which were: *Somnolence/tiredness, dizziness, ataxia, irritability, falls, cognitive slowing, depression, nausea*, and one "*other*" category. Finally, the information on the maintenance dose for PER or LCM achieved at 6 months was to be recorded, in milligram per day.