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Efficacy and safety of levetiracetam as adjunctive therapy in adult patients with uncontrolled partial epilepsy: The Asia SKATE II Study

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ABSTRACT

This study evaluated the safety and efficacy of levetiracetam as adjunctive therapy for partial seizures in everyday clinical practice in Asian populations. Patients aged ≥16 years ($N=251$) with inadequately controlled partial epilepsy were recruited from 29 centers across Asia. Levetiracetam was added to existing antiepileptic medication for 16 weeks at a starting dose of 500 or 1000 mg/day and titrated to a maximum of 3000 mg/day according to clinical response. The study completion rate was 86.9%. Adverse events were reported by 73.3% of patients and were generally mild, leading to treatment withdrawal in only 7.2%. The most common adverse events were somnolence (30.3%) and dizziness (14.7%). Compared with pretreatment baseline, 44.0% of patients had a ≥50% reduction in seizure frequency, with a median reduction of 46.4%, and 17.7% became seizure free during the treatment period. Levetiracetam was well tolerated and efficacious as adjunctive therapy for partial epilepsy in clinical practice among Asian populations.

1. Introduction

Levetiracetam (Keppra, UCB Pharma SA, Belgium) is believed to exert its antiepileptic properties by binding specifically to synaptic vesicle protein 2A [1], thereby interfering with synaptic vesicle exocytosis and neurotransmitter release [2]. Based on the results from pivotal double-blind trials conducted in the United States and Europe [3–5], its use as add-on therapy for partial-onset seizures in adults was approved by the U.S. Food and Drug Administration in 1999 and by the European Medicines Agency in 2000. In Asia, similar double-blind randomized trials have also been performed in Japan [6], China [7] and Taiwan [8], although relatively fewer patients were involved (Japan 143, China 103, Taiwan 47 randomized to levetiracetam).

Because of their restrictive design, results from regulatory trials may not be directly applicable to the clinical setting [9]. For instance, patients recruited to these studies usually have a high baseline seizure frequency and have previously failed a large number of antiepileptic drugs (AEDs). Furthermore, in clinical practice, dosage is adjusted according to treatment response, whereas in regulatory trials fixed doses are usually used. Therefore, to aid translation of findings from regulatory trials into everyday clinical practice, a number of open-label observational studies have been performed. However, a recent systematic review of observational add-on AED studies identified marked heterogeneity and publication bias among the studies [10]. This might have resulted from their wide variation in designs and settings, limiting meaningful comparison of findings across the studies. It is also notable that none of the studies reporting on levetiracetam were conducted in Asia.

To overcome this limitation, a series of phase IV, prospective, open-label, community-based studies of levetiracetam as add-on therapy for partial epilepsy have been conducted under a unified protocol. Their aim was to further evaluate the efficacy and safety of levetiracetam and to obtain additional information about its optimal use in populations that more closely reflect patients encountered by

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physicians around the world in their daily clinical practice. Results from the KEEPER study (Keppra® Epilepsy Evaluation of the Patient Time to Response, $N = 1030$) performed in the United States [11–13] and the SKATE study (Safety of Keppra as Adjunctive Therapy in Epilepsy, $N = 1541$) in Europe, Australia, Argentina, and Mexico [14] have been reported. A similar study has also been conducted in Korea [15] with a relatively small number of patients ($N = 100$). Here, we present results from a similarly designed multicenter, multicountry study, which included the largest number of patients treated with levetiracetam in a single study in Asia to date.

2. Methods

2.1. Study population

The Asia SKATE II study (N01036, ClinicalTrials.gov identifier NCT00160654) was conducted in six Asian countries/regions (Hong Kong, Malaysia, the Philippines, Singapore, Taiwan, and Thailand). The study enrolled Asian patients aged at least 16 years with inadequately controlled partial seizures (with or without secondary generalization) which were classifiable according to the International Classification of Epileptic Seizures [16]. To be eligible for the study, patients must have been receiving one or two concomitant AEDs at stable doses for at least 4 weeks prior to selection, and must have had between 3 and 42 partial seizures over the 3-month period prior to selection. Females of childbearing potential were required to use a reliable form of contraception.

Exclusion criteria included previous exposure to levetiracetam; participation in another clinical trial within 12 weeks of the selection visit or at any time during this trial; serious psychiatric disorder within the past 5 years; pseudoseizures within the past year; progressive neurological disease; and unaccountable seizures or history of convulsive status epilepticus within the past 5 years. Patients with absolute neutrophil count $<1800/mm^3$ or platelet count $<100{,}000/mm^3$ were also excluded.

Written informed consent was obtained from all patients (or parent/guardian) prior to initiation of study procedures.

2.2. Study design

This phase IV study was a multicountry, multicenter, open-label, single-arm study. The study started on 24 November 2003 and finished on 12 December 2006.

Similar to the KEEPER [11–13] and SKATE [14] studies, the Asia SKATE II study consisted of a selection visit (week 0) and a 16-week treatment period (including 4 weeks of uptitration and 12 weeks at stable dose) (Fig. 1). At the selection visit, demographic information and details of medical history, epilepsy etiology, and AED history were collected. A retrospective historical seizure count over the past 3 months was recorded, based on daily diary entries where possible. Physical and neurological examinations were conducted and blood samples were taken for routine safety laboratory evaluations. Patients initially received levetiracetam 1000 mg/day twice daily (or a lower dose of 500 mg/day for the first week at the investigator's discretion) in addition to their existing regimen of one or two concomitant AEDs. Study visits were planned after 2, 4, 10, and 16 weeks of treatment. Based on seizure control and tolerability, levetiracetam dosage could be adjusted from week 2 in 500 or 1000 mg/day increments to a maximum of 3000 mg/day. Downtitration was allowed if required for safety reasons. In patients with mild to moderate renal impairment, the daily dose was individualized according to renal function based on creatinine clearance [17]. At week 16, patients were given the opportunity to continue on levetiracetam treatment or to enter a downtitration period followed by a safety visit.

The study was conducted in accordance with the ICH Note for Guidance on Good Clinical Practice and the principles that have their origin in the Declaration of Helsinki [18], and local regulatory requirements. The protocol and informed consent form were approved by independent ethics committees of the participating centers.

2.3. Assessments

Adverse events (AEs) were continuously monitored throughout the study, based on investigator observation and spontaneous patient reports. Details of all seizures experienced during the study were recorded on daily record cards by patients. At each visit, these were verified and classified by the investigator according to the International Classification of Epileptic Seizures [16]. A 7-point Global Evaluation Scale (GES) was completed by the investigator at the end of the treatment period (week 16) or at treatment discontinuation, according to their assessment of change in the severity of the patient's condition over the duration of the study.

2.4. Statistical analysis

The intent-to-treat (ITT) population consisted of all subjects enrolled who took at least one dose of study medication. All safety and efficacy data were summarized descriptively for the ITT population. Mean weekly frequencies of partial seizures and all seizure types were calculated over the 3-month historical baseline period. Efficacy data were assessed for partial seizures and all seizure types as median percentage reduction from baseline in weekly seizure frequency, ≥50% responder rate (defined as proportion of patients who had at least 50% reduction in seizure frequency from baseline), and seizure freedom rate (100% reduction in seizure frequency from

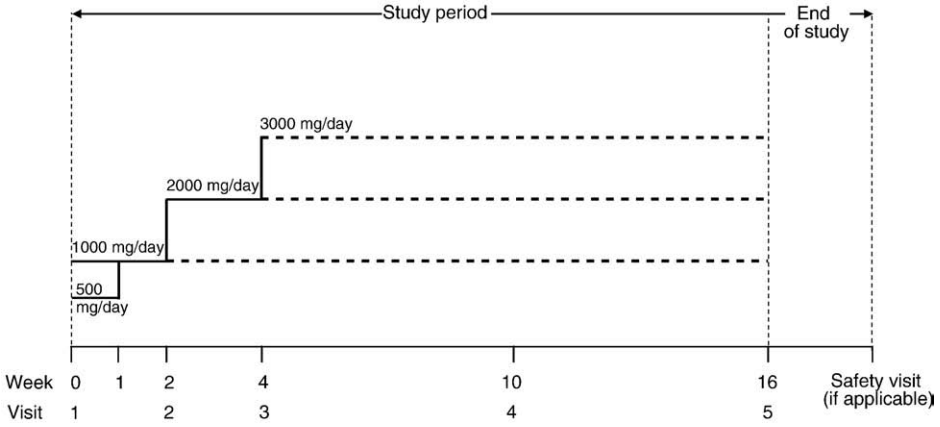

Fig. 1. Study design.