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Original article

Long-term efficacy and safety of lamotrigine monotherapy in Japanese and South Korean pediatric patients with newly diagnosed typical absence seizures: An open-label extension study

Sawa Yasumoto [a,1], Yoko Ohtsuka [b,2], Katsuaki Sato [c], Atsuyo Kurata [c], Yotaro Numachi [c], Masahiro Shimizu [c,*]

[a] *Department of Pediatrics, School of Medicine, Fukuoka University, Fukuoka, Japan*
[b] *Department of Child Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan*
[c] *GlaxoSmithKline, Tokyo, Japan*

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Abstract

Purpose: To investigate the efficacy and safety of long-term lamotrigine (LTG) monotherapy in Japanese and South Korean pediatric patients with newly diagnosed typical absence seizures.

Methods: Six Japanese patients and one South Korean patient were enrolled in the extension phase of the study after completing the 12-week maintenance phase of an open-label clinical study of LTG monotherapy. During the extension phase, patients underwent efficacy and safety evaluation every 12 weeks.

Results: Of the seven patients, six patients completed the extension phase. The seizure-free rate confirmed by hyperventilation (HV)-electroencephalography ranged from 71.4% to 100.0% at each visit up to Week 168 of the extension phase. Similar effects were confirmed by HV-clinical signs and seizure diaries. Although no unexpected adverse events were observed, one Japanese patient was withdrawn from the extension phase due to mild drug-related rash developed 842 days after the start of LTG.

Conclusion: Although the number of patients is limited, long-term LTG monotherapy appeared to be effective and generally well tolerated in Japanese and South Korean pediatric patients with typical absence seizures.

Keywords: Lamotrigine; Long-term monotherapy; Typical absence seizures; Children; Efficacy; Safety

1. Introduction

Lamotrigine (LTG) was approved in Japan in 2008 as an adjunct therapy for the treatment of partial seizures including secondarily generalized seizures, generalized tonic-clonic seizures and generalized seizures in Lennox-Gastaut syndrome in adults and children. There were no clinical experiences of LTG therapy for typical absence seizures in Japanese patients at that time. In

* Corresponding author at: GlaxoSmithKline, Akasaka Intercity AIR, 1-8-1 Akasaka, Minato-ku, Tokyo 107-0052, Japan.
E-mail address: masahiro.2.shimizu@gsk.com (M. Shimizu).
[1] Current affiliation: Department of Medical Education Center, School of Medicine, Fukuoka University, Fukuoka, Japan.
[2] Current affiliation: Department of Child Neurology, Asahigawaso Rehabilitation and Medical Center, Okayama, Japan.

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September 2011, we started an open-label study to assess the efficacy and safety of LTG monotherapy in Japanese and South Korean pediatric patients with newly diagnosed typical absence seizures. In our previous report [1], we showed the efficacy and safety of LTG monotherapy during the dose escalation phase, 12 weeks of the maintenance phase and the following 12 weeks of the extension phase in the study. Based on the primary data in our previous report [1], LTG monotherapy was approved at a maintenance dose of 1–10 mg/kg/day not to exceed a maximum of 200 mg/day for use in children with typical absence seizure in September 2015 in Japan. Although the study allowed treatment at up to 400 mg/day, 200 mg/day has been selected as the maximum approved dose in Japan based on the facts that the modal dose exceeded 200 mg/day in only two patients in the study and the maximum approved dose in Europe is 200 mg/day. As for long-term outcomes for LTG monotherapy for typical absence seizures in other countries, Coppola et al. [2] and Glauser et al. [3] reported the long-term outcome up to 12 months. On the other hand, there were no experiences of long-term outcomes for LTG monotherapy for typical absence seizures in Japanese and South Korean patients. Our study was continued until approval of LTG monotherapy in Japan for the treatment of typical absence seizures in children. We report the efficacy and safety of long-term treatment with LTG monotherapy for typical absence seizures over a more than two-year period.

2. Subjects and methods

This study was conducted as an extension of the initial phase III study (a multi-center, uncontrolled open-label study, ClinicalTrials.gov Identifier NCT01431976) to assess the efficacy and safety of LTG monotherapy in children and adolescents with newly diagnosed typical absence seizures. Patients with newly diagnosed typical absence seizures were enrolled who had clinical signs of typical absence seizures and also electroencephalography (EEG) findings (a burst of $\geqq$3 s of 2.5–4.5 Hz generalized spike-and-wave or multiple spike-and-wave activity during the awake state) on one of two 4-minute hyperventilation (HV) tests. The details of eligible criteria and LTG dose regimens of the initial study has been described previously [1]. Among those who completed the maintenance phase of the study, patients who had responded positively to LTG monotherapy without tolerability issues were deemed eligible to enter the extension phase. Eligible patients entered the extension phase if they required continued LTG treatment in the investigator's judgment and if their parent(s) or legal guardian(s) wished to have the treatment continued. Written informed consent was obtained again from their parent(s) or legal guardian (s) and from patients who were able to understand the concepts and procedures of the study.

During the extension phase, patients visited the clinic every 12 weeks for efficacy and safety assessment. If discontinuation of LTG was determined during the extension phase, the patient promptly entered a taper phase and then underwent a post-study examination for ensuring the safety within 1–4 weeks after the last dose of LTG. Patients who entered the extension phase could continue the study until approval of LTG monotherapy in Japan for typical absence seizures in children. Patients continued the maintenance phase regimen during the extension phase. The dose of LTG could be adjusted as necessary within the range of 1.2–10.2 mg/kg/day (maximum dose: 400 mg/day) based on seizure status and safety. LTG was administered once a day in the evening. If the number of tablets was too much, administration could be divided into two doses in the morning and evening.

Efficacy endpoints of the extension phase were the proportion of patients confirmed to be seizure free by HV-EEG or by HV-clinical signs, which was calculated along with the associated 95% confidence intervals, and the number of days per week with seizures from a seizure diary. The status of typical absence seizures was confirmed by clinical signs of typical absence seizures during HV tests (e.g., staring or impairment of consciousness) and EEG findings by 4-minute HV tests. EEG definition of a typical absence seizure was as follows: a burst of $\geqq$3 s of 2.5–4.5 Hz generalized spike-and-wave or multiple spike-and-wave activity during the awake state on EEG. Confirmation by HV-EEG was conducted every 24 weeks after Week 24 of the extension phase, and confirmation by HV-clinical signs, every 24 weeks after Week 12 of the extension phase. The number of days per week with seizures was determined for the entire extension phase from a seizure diary. Safety endpoints of the extension phase included adverse events, clinical laboratory data, vital signs (blood pressure and pulse rate), body weight, and 12-lead electrocardiogram (ECG).

The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice and the principles of the Declaration of Helsinki, after obtaining approval from the institutional review boards at all sites.

3. Results

After completion of the maintenance phase, six patients in Japan and one patient in South Korea entered the extension phase. One Japanese patient was withdrawn from the study because of an adverse event (rash), while six patients completed the extension phase. The details of the seven patients are described in Table 3. The duration of LTG treatment including the initial

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