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Case Report

Evaluation of perampanel as monotherapy for focal seizures: Experience from open-label extension studies

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ABSTRACT

Perampanel, a selective, non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist, is approved for adjunctive treatment of focal seizures, with or without secondarily generalized seizures, and for primary generalized tonic–clonic seizures in patients with epilepsy aged ≥12 years. Perampanel was recently approved for monotherapy use for focal seizures in the U.S.A. Anti-seizure drug monotherapy may be preferable to polytherapy, which is generally associated with increased toxicity, non-compliance, and cost. Here, we report cases where patients had converted to perampanel monotherapy during open-label extension (OLEx) portions of 9 Phase II and III studies.

Of 2245 patients who enrolled in the OLEx studies, we identified 7 patients with drug-resistant focal seizures who discontinued all non-perampanel anti-seizure drugs and were maintained on perampanel monotherapy for ≥91 days until the end of data cut-off. Patients received perampanel monotherapy for up to 1099 days (157 weeks), most at a modal dose of 12 mg. Seizure data were available for 6 patients, of whom 5 had a ≥90% reduction in overall seizure frequency between baseline and their last 13-week period of monotherapy (3 were seizure-free). Perampanel monotherapy was generally well tolerated and the safety profile during perampanel monotherapy was consistent with clinical and post-marketing experience in the adjunctive setting. This analysis included a small proportion of patients with highly drug-resistant focal seizures who converted to monotherapy during OLEx studies. While these limited data are encouraging in suggesting that perampanel might be useful as a monotherapy, further studies are required to explore outcomes in a less drug-resistant population, where a larger proportion of patients might benefit from monotherapy.

1. Introduction

Perampanel, a selective, non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist, is approved for adjunctive treatment of focal seizures, with or without secondarily generalized (SG) seizures, and for primary generalized tonic–clonic seizures in patients with epilepsy aged ≥12 years [1,2]. Perampanel was recently approved for monotherapy use for focal seizures in the U.S.A.

It has been a regulatory standard for anti-seizure drugs to be initially evaluated for adjunctive use, given ethical concerns around the use of placebo-controlled trials for anti-seizure drug monotherapy [3].

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; bid, twice daily; FDA, Food and Drug Administration; OLEx, open-label extension; qam, every morning; qd, once daily; qhs, every night at bedtime; qpm, every evening; SG, secondarily generalized; TEAE, treatment-emergent adverse event; tid, three times daily.

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However, since anti-seizure drug polytherapy is often associated with increased toxicity, non-adherence, and cost, monotherapy may be preferable in some clinical practice settings [4].

Despite challenges in trial design, many anti-seizure drugs have demonstrated efficacy as monotherapies [5]. In the U.S.A., several anti-seizure drugs have had their original indications expanded to include use in monotherapy settings, including lacosamide, lamotrigine extended release, and topiramate. Furthermore, the arguments of a white paper has recently advocated a unified indication for anti-seizure drugs, irrespective of concomitant anti-seizure drug use [3], and as a consequence, the Food and Drug Administration (FDA) has determined that it is acceptable to extrapolate data from adjunctive trials to the monotherapy setting.

Here, we report data from patients who converted to perampanel monotherapy during the open-label extension (OLEx) portions of Phase II and Phase III adjunctive studies. This analysis explores our understanding around the conversion to perampanel monotherapy for the treatment of focal seizures. In addition, and based on the FDA policy around extrapolation of adjunctive data to the monotherapy setting, these data formed part of the data that were submitted to the FDA, supporting the approval of perampanel monotherapy in the U.S.A. for the treatment of focal seizures (with or without SG seizures) in patients with epilepsy aged ≥ 12 years [2,6]. These data have also been submitted to the European Medicines Agency as part of the data in support of an amendment to the perampanel *Summary of Product Characteristics* to include monotherapy data in the *Clinical Section*.

2. Methods

The clinical development of perampanel as an adjunctive treatment included 9 Phase II and III studies in patients receiving 1–3 concomitant anti-seizure drugs. Eight were randomized, double-blind, placebo-controlled studies in patients with drug-resistant focal seizures, with or without SG seizures (Studies 206 [NCT00144690] and 208 [NCT00416195]: patients aged 18–70 years; Studies 304 [NCT00699972], 305 [NCT00699582], 306 [NCT00700310], and 335 [NCT01618695]: patients aged ≥12 years; and Study 235 [NCT01161524]: adolescent patients aged ≥12 to ≤17 years) [7–11], or primary generalized tonic–clonic seizures and idiopathic generalized epilepsy (Study 332 [NCT01393743]: patients aged ≥12 years) [12]. The remaining study was an open-label, dose-escalation Phase II study of adjunctive perampanel as an oral suspension in patients from the U.S.A. aged 2 to <12 years with any seizure type (Study 232 [NCT01527006]).

All studies were performed in accordance with the Declaration of Helsinki, European Medicines Agency requirements, the U.S. Code of Federal Regulations, and the ICH-E6 Guideline for Good Clinical Practice. All participants gave written informed consent.

Patients who completed 1 of these studies could receive adjunctive perampanel (daily dose of up to 12 mg) in 1 of the following OLEx studies:

- Study 207 (patients enrolled from Studies 206 and 208; $n = 138$) [13]
- Study 307 (patients enrolled from Studies 304, 305, and 306; $n = 1218$) [14]
- Study 335 OLEx ($n = 596$)
- Study 235 OLEx ($n = 114$)
- Study 332 OLEx ($n = 138$)
- Study 232 OLEx ($n = 41$).

In all OLEx studies, concomitant anti-seizure drugs could be adjusted in dose or changed as clinically dictated (e.g., removed if seizures were well controlled with perampanel). Therefore, although perampanel monotherapy was not an objective, it was a possibility if all non-perampanel anti-seizure drugs were discontinued.

This analysis included patients who discontinued all non-perampanel anti-seizure drugs during 1 of the OLEx studies, received perampanel as monotherapy for at least 91 days, and were able to continue monotherapy thereafter (until the relevant data cut-off date for each individual OLEx study). The time period of 91 days was selected with the aim of identifying cases where there was a clear decision to attempt conversion to monotherapy and to exclude cases where non-perampanel anti-seizure drugs were temporarily discontinued over a shorter period of time for any other reason (e.g., due to tolerability reasons or patient non-adherence). Throughout the studies, median percent change in seizure frequency per 28 days from pre-perampanel baseline was assessed and patients were monitored for treatment-emergent adverse events (TEAEs).

3. Results

3.1. Patients

Overall, 2245 patients with drug-resistant seizures, despite treatment with 1–3 concomitant anti-seizure drugs, were enrolled in the OLEx studies. Of these, 9 patients discontinued all concomitant anti-seizure drugs and took perampanel as monotherapy for at least 91 days.

Of these 9 patients, 7 continued to receive perampanel as monotherapy until data cut-off, and so met the criteria for inclusion in the present analysis. Six of these patients had received perampanel monotherapy in Study 307 (Patients 1–6), and 1 in the Study 235 OLEx (Patient 7). Five patients had received placebo in the double-blind treatment phase of the Core Study (Patients 1, 3, 4, 6, and 7) and 2 had received a non-effective dose of perampanel 2 mg (Patients 2 and 5), although all received an optimized perampanel dose in the OLEx studies. At baseline of the double-blind treatment phase, patients had been receiving 1 concomitant anti-seizure drug (Patients 3, 4, 5, and 7), 2 concomitant anti-seizure drugs (Patients 1 and 6), or 3 concomitant anti-seizure drugs (Patient 2).

The 7 patients comprised 1 female and 6 male patients, with an age range of 15–40 years. At baseline of the double-blind treatment phase, time since diagnosis of epilepsy ranged from 2.8 to 21.9 years, and seizure frequency per 28 days ranged from 0.5 to 93.8. Three patients had been experiencing focal seizures with motor signs (Patients 3, 4, and 5), 1 had been experiencing focal seizures without motor signs (Patient 1), 2 had been experiencing focal seizures with secondary generalization (Patients 4 and 6), and 5 had been experiencing focal impaired awareness seizures (complex partial seizures in the previous ILAE classification; Patients 1, 2, 5, 6, and 7).

The other 2 patients, who received perampanel monotherapy for 91 days, later reverted back to polytherapy (reasons for discontinuation of perampanel monotherapy unknown); these patients were not included in the analysis because they did not meet the pre-defined requirement for monotherapy to have continued until data cut-off. One of these patients was a 58-year-old female who received perampanel for 1126 days in Study 307, including 123 days as monotherapy (modal daily dose = 12 mg); during the only 13-week window where monotherapy was received throughout (Weeks 79–91 of perampanel treatment), this patient had a 68.4% reduction in seizure frequency compared with baseline. The other patient was a 6-year-old female who received perampanel for 287 days in the Study 232 OLEx, including 103 days as monotherapy (modal daily dose = 0.2 mg/kg); during the only 13-week window where monotherapy was received throughout (Weeks 27–39 of perampanel treatment), this patient had an 87.7% reduction in seizure frequency compared with baseline.

3.2. Perampanel treatment

Fig. 1 summarizes the time courses of treatment with perampanel and concomitant anti-seizure drugs in Patients 1–7. Patients received