Perampanel with concomitant levetiracetam and topiramate: Post hoc analysis of adverse events related to hostility and aggression

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1. Introduction

Perampanel is an orally administered, highly selective, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor antagonist [1,2]. Approved for adjunctive treatment of partial seizures, with or without secondarily generalized seizures, and for primary generalized tonic–clonic seizures (PGTCS) in patients with epilepsy aged ≥12 years [1,3], perampanel was studied in 4 double-blind, placebo-controlled Phase III clinical trials published between 2012 and 2015 [4–7]. Perampanel was recently approved for monotherapy use for partial seizures in the US. Three of these Phase III studies (Studies 304, 305, and 306) were 19 weeks in duration and were conducted in patients with drug-resistant partial seizures, with or without secondarily generalized seizures, who were receiving 1 to 3 concomitant antiepileptic drugs (AEDs). In all 3 partial seizure studies, perampanel, at once-daily doses ranging from 4 mg to 12 mg, demonstrated statistically superior efficacy compared to placebo in reducing seizure frequency and was generally well tolerated [5–7]. The fourth Phase III study (Study 332) was 17 weeks in duration and was conducted in patients with drug-resistant PGTCS receiving 1 to 3 concomitant AEDs. Treatment with perampanel was well tolerated and, as in the partial seizure studies, resulted in a significantly greater reduction in seizure frequency compared to placebo [4]. Although treatment with perampanel was well tolerated overall in the Phase 3 studies, the US Prescribing Information for perampanel includes a boxed warning for serious psychiatric and behavioral reactions [1,7]. These reactions include “agression, hostility, irritability, anger, and homicidal ideation and threats,” and have been observed in patients...
both with and without concomitant use of medications associated with hostility and aggression [1,8]. Additionally, the Warnings and Precautions section of the Prescribing Information notes that patients treated with perampanel have experienced “more hostility- and aggression-related adverse reactions that were serious, severe, and led to dose reduction, interruption, and discontinuation more frequently than placebo-treated patients” [1]. Ettinger et al. conducted an in-depth post hoc analysis of the safety data from perampanel Phase II and III studies in patients with partial seizures and patients without epilepsy and Phase I patients/volunteers [8]. This analysis demonstrated a dose-related increase in psychiatric TEAEs in patients with partial seizures treated with perampanel at doses of up to 12 mg, while aggression and anger were observed at minimal rates in the patients without epilepsy who were treated with perampanel at doses of up to 8 mg, or in the Phase I patients/volunteers who were treated with perampanel at doses greater than 12 mg [8].

It is important to note that adverse events (AEs) such as aggression and irritability are not exclusive to perampanel. These AEs have been observed with other commonly prescribed AEDs, including levetiracetam and topiramate, which are both approved for the treatment of partial seizures and PGTCS [9,10]. In the case of levetiracetam, the Warnings and Precautions section of the US Prescribing Information warns of the risk of “behavioral abnormalities and psychotic symptoms,” while also noting that levetiracetam-treated patients are at risk for irritability and aggression [9]. In comparison, topiramate differs in its potentially more mild AE profile and behavioral effects [10]. The fact that these widely used agents confer differing risk profiles for behavioral AEs offers a rationale for comparing related safety outcomes when topiramate or levetiracetam is used in conjunction with perampanel and whether any effects are cumulative. Thus, the purpose of the present study is to evaluate the occurrence of hostility- and aggression-related AEs in the 3 perampanel Phase III partial seizure studies and the Phase III PGTCS study in patients who received perampanel therapy and concomitant treatment with levetiracetam and/or topiramate.

2. Material and methods

2.1. Phase III trials in partial seizures

The design of the 3 Phase III studies of perampanel (Study 304, NCT00699972; Study 305, NCT00699582; and Study 306, NCT00700310) has been described in detail elsewhere [5–7]. Briefly, inclusion criteria required patients to be at least 12 years old, with a diagnosis of simple or complex partial onset seizures, with or without secondary generalization, according to the 1981 Classification of Epileptic Seizures from the International League Against Epilepsy [11]. Patients were required to have uncontrolled partial onset seizures despite treatment with at least 2 different AEDs within the previous 2 years. Patients were also required to have experienced at least 5 partial seizures while receiving up to 3 AEDs at a stable dose during the 6-week baseline period [5–7].

In each study, patients entered the Pre-randomization Phase and were assessed for baseline seizure frequency and eligibility. Following the 6-week Baseline Period, patients were randomized to placebo or perampanel 2, 4, 8, or 12 mg [5–7]. During the 6-week Titration Period, the perampanel dose was increased by 2 mg per week, from 2 mg/day to the randomly assigned dose, or to the maximum tolerated dose (MTD) if the patient could not tolerate the randomly assigned dose. Patients continued on the dose achieved during titration throughout the 13-week Maintenance Period; they also continued receiving their established concomitant AEDs without modification. Patients completing the Maintenance Period were invited to enter a long-term, open-label extension study. Those who discontinued treatment or who did not enter the extension study had a follow-up visit 4 weeks after the end of therapy [5–7].

2.2. Phase III trial in primary generalized tonic–clonic seizures (PGTCS)

The Phase III study to evaluate the efficacy and safety of adjunctive perampanel in PGTCS (Study 332, NCT01393743) has been described in detail elsewhere [4]. Patients in this trial were at least 12 years old and had a clinical diagnosis of PGTCS in the setting of idiopathic generalized epilepsy, with or without other subtypes of primary generalized seizures. Patients also had to have experienced at least 3 PGTCS seizures during the 8 weeks prior to randomization. Eligible patients were receiving fixed doses of 1–3 AEDs during the 30 days prior to baseline.

The Pre-randomization Phase consisted of 2 periods: Screening (up to 4 weeks) and Baseline (4 or 8 weeks), determined based on the reliability of patients’ own records of their seizures during the Screening Period), during which patients were assessed for eligibility to participate in the study. The Randomization Phase consisted of 3 periods: Titration (4 weeks), Maintenance (13 weeks), and Follow-up (4 weeks; only for those patients not enrolling in the Extension Phase). At the start of the Randomization Phase, eligible patients were randomized to the perampanel- or placebo-treatment groups in a 1:1 ratio. During the 4-week Titration Period, patients initially received perampanel 2 mg/day or matching placebo and were up-titrated weekly in 2-mg increments to a target dose of 8 mg/day or the MTD. At the completion of the Titration Period, patients entered the 13-week Maintenance Period on the last dose level achieved at the end of the Titration Period and continued taking this dose once daily for the duration of the Maintenance Period unless adjustments were deemed necessary by the investigator [4]. Patients were invited to enter a 142-week open-label extension. Those who chose not to enter the extension study, or who discontinued treatment during the Maintenance Period, immediately entered the 4-week Follow-Up Period.

2.3. Determination of hostility- and aggression-related events

Both serious and non-serious treatment-emergent AEs (TEAEs) were determined based on the Medical Dictionary for Regulatory Activities (MedDRA) standard MedDRA query (SMQ) for hostility- and aggression-related events. The “Narrow” SMQs describe TEAEs most likely to reflect a condition of interest. For the present assessment, these would include TEAEs such as aggression, anger, belligerence, or physical assault. “Broad” SMQs identify all possible events, including those that may be of little or no interest, such as skin laceration. A “Narrow & Broad” SMQ search includes both categories of terms [12,13]. Relevant medical history (i.e., prior psychiatric and/or aggression history) and concomitant use of levetiracetam and topiramate were reported for those patients with TEAEs identified via the hostility- and aggression-related “Narrow” and “Narrow & Broad” SMQs.

3. Results

3.1. Patient disposition

The pooled patient population who entered the double-blind phases of their respective partial seizure studies included 1480 patients: 1038 receiving perampanel and 442 receiving placebo. In the PGTCS study, 163 patients were treated during the double-blind phase: 81 received perampanel and 82 received placebo. Table 1 displays the number of patients in all 4 Phase III studies receiving concomitant levetiracetam (+ LEV) or not (− LEV), receiving concomitant topiramate (+ TOP) or not (− TOP), or receiving both AEDs (+ LEV/+ TOP), or not taking both (− LEV/− TOP). Note that there is overlap between groups. In addition to these agents, patients might have been receiving other AEDs, considering the study inclusion criteria called for baseline use of 1 to 3 concomitant AEDs. Although a change in concomitant AEDs was not allowed, several patients did not comply due to multiple reasons. For example, in the LEV group, 1 patient discontinued on Day 44 and another took LEV only as a rescue medication. In the TOP group,
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