Epilepsy & Behavior Case Reports 10 (2018) 114–117

Contents lists available at ScienceDirect

Epilepsy & Behavior Case Reports

journal homepage: www.elsevier.com/locate/ebcr

Case Report

Adjunctive perampanel for glioma-associated epilepsy☆

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ARTICLE INFO

Article history:
Received 18 July 2018
Received in revised form 3 September 2018
Accepted 4 September 2018
Available online 9 October 2018

Keywords:
Epilepsy
Seizure
Brain tumor
Glioma
Isocitrate dehydrogenase 1
Perampanel

ABSTRACT

Glioma-associated epilepsy is associated with excessive glutamate signaling. We hypothesized that perampanel, an amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptor antagonist, would treat glioma-related epilepsy. We conducted a single-arm study of adjunctive perampanel for patients with focal-onset glioma-associated seizures. The most common related adverse events were fatigue and dizziness. Three out of 8 participants had self-reported seizure reduction and an additional 3 reported improved control. Of these 6, 5 had isocitrate dehydrogenase 1 mutant gliomas. We conclude that perampanel is safe for patients with glioma-related focal-onset epilepsy. Further study into the association between AMPA signaling, IDH1 status and seizures is warranted.

1. Introduction

Nearly one-third of patients with primary brain tumors experience a seizure as the presenting symptom and another 30–50% develop seizures during their disease course [1]. Moreover, many of these patients have epilepsy that adversely affects quality of life. In fact, seizure control is the most important predictor of quality of life in recurrent low-grade glioma patients [2]. A challenge of treating brain tumor-related epilepsy is that anti-seizure drug (ASD) options are limited due to interactions with chemotherapy and side effects including cognitive dysfunction in an already susceptible patient population. Therefore, there is a real need to find effective ASDs that are without cytochrome P450 enzyme induction properties that are well tolerated.

Glutamate is the chief excitatory neurotransmitter in the central nervous system and is pro-epileptogenic. In murine models, glutamate release was found to be responsible for epileptic activity [3]. Aberrant glutamate regulation is associated with primary brain tumor-associated epilepsy. Specifically, glioma peritumoral tissue contains increased extracellular glutamate concentrations due to increased glioma cell glutamate secretion via cystine–glutamate transporters and impaired glutamate reuptake by surrounding reactive astrocytes [4,5].

Perampanel is a highly selective non-competitive-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptor antagonist without enzyme-inducing properties. It is U.S. Food & Drug Administration (FDA) approved as an adjunct and as monotherapy for focal-onset seizures and treatment of partial-onset seizures with or without secondarily generalized seizures as adjunct or monotherapy and primary generalized tonic-clonic seizures as adjunct therapy in patients with epilepsy who are ≥12 years of age We hypothesized that perampanel would be a viable option for treatment of focal-onset seizures in patients with brain tumors, especially given the presence of excess glutamate within the glioma microenvironment. We therefore conducted a single-arm prospective study to assess the safety, tolerability and efficacy of perampanel as an adjunctive ASD in patients with gliomas who have focal-onset seizures.

2. Methods

This trial (Duke University institutional review board (IRB) approval Pro00055609; ClinicalTrials.gov identifier: NCT02363933) was conducted at the Preston Robert Tisch Brain Tumor Center at Duke University, Durham, North Carolina, United States. This protocol was reviewed and approved by the FDA and the Duke University IRB. The study was conducted in accordance with the Declaration of Helsinki, Belmont Report, U.S. Common Rule guidelines, and the International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS). Before participation, all patients signed a written informed consent.

2.1. Participants

Adult subjects aged 18 and older were eligible if diagnosed with a primary glioma and had focal-onset seizure activity, which was defined

☆ **Funding**: Eisai, Inc., Woodcliff, NJ 07677 provided funding support.
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https://doi.org/10.1016/j.ebcr.2018.09.003

as ≥3 seizures in a 28-day period, and on a non-enzyme inducing antiseizure regimen. Eligibility criteria also included a Karnofsky performance scale index (KPS) of ≥70% and satisfactory hematologic, renal, and liver function. Subjects were excluded if they were pregnant or breastfeeding, had a known allergy to perampanel, concomitant use of a cytochrome P450 inducer, an unstable psychiatric diagnosis, such as a history of previous suicidal or homicidal ideation, depression or mood disturbances leading to hospitalization or chronic excessive use of psycho-pharmaceuticals, alcohol, illicit drugs, or narcotics.

2.2. Study design

This was a single-arm prospective study. In the original design of the study, perampanel was to be started at a dose of 2 mg/day and to be up-titrated weekly, in 2 mg increments, to a target dose of 8 mg/day. After a total of 16 weeks on therapy, perampanel was to be tapered down by 2 mg/day every week until the subject was no longer taking perampanel at week 20. This was done for the first 4 subjects but the study was amended to up-titrate perampanel more slowly in 2-week intervals rather than in 1-week intervals. Additionally, the amendment changed the maximum dose to be determined by seizure control rather than the specific dose such that if a subject obtained seizure control then maximum dose could be as low as 4 mg/day and up to 8 mg/day. The amendment was due to fatigue and dizziness seen in the initial 4 subjects at the presumed rapid interval change (1 week vs 2 weeks). Participants were assessed at time of enrollment, 8 weeks, 16 weeks, and 24 weeks. Assessments included a physical examination, neurological examination, and evaluation of seizure history.

2.3. Outcome

The primary objective of this study was to assess the efficacy of perampanel as an adjunct ASD in patients with primary glioma and focal-onset seizures. The secondary objective was to evaluate the percentage of subjects with unacceptable adverse events related to perampanel treatment.

Table 2
Adverse events possibly, probably or definitely related to perampanel.

	All grades n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 5 n (%)
Nausea	1 (13)	1 (13)	0 (0)	0 (0)
Fatigue	5 (63)	4 (50)	1 (13)	0 (0)
Dizziness	2 (25)	2 (25)	0 (0)	0 (0)
Somnolence	1 (13)	1 (13)	0 (0)	0 (0)
Confusion	1 (13)	1 (13)	0 (0)	0 (0)

2.4. Statistical analyses

Seizure frequency was estimated separately for each patient within the titration, treatment, tapering, and follow-up phases of treatment, and a descriptive analysis of seizure frequency on treatment was conducted. Socio-demographic and clinical characteristics as well as genotype status of subjects receiving perampanel on this study were summarized. All subjects who received perampanel were included in the safety and efficacy analysis set.

3. Results

Eight subjects were enrolled and received drug on the study. Subject characteristics are summarized in Table 1. The median age was 45 years. Glioma subtypes consisted of glioblastoma (n = 2), anaplastic astrocytoma (n = 2), oligodendroglioma (n = 2) and diffuse astrocytoma (n = 2). Isocitrate dehydrogenase 1 (IDH1) genotype status was available for 7 participants. Five had IDH1 mutant tumors and 2 had tumors with wild-type IDH1. Additionally, all subjects with documented

Table 1
Subject characteristics.

Subject	Age	Gender	KPS	Tumor type/location	Molecular markers	Concurrent ASDs
1	50	M	90	Left frontal ODG (WHO grade II)	IDH1: mutant MGMT: methylated TERT: wild-type 1p/19q: co-deleted	LEV
2	53	M	70	Left frontotemporal AA (WHO grade III)	IDH1: mutant MGMT: methylated TERT: wild-type 1p/19q: not performed	LEV
3	40	M	90	Right parietal astrocytoma (WHO grade II)	IDH1: wild-type MGMT: unknown TERT: unknown 1p/19q: unknown	LEV, DZP, LZP
4	38	M	80	Left temporal astrocytoma (WHO grade II)	IDH1: mutant MGMT: methylated TERT: wild-type 1p/19q: intact	LEV, LZP
5	61	M	80	Left frontoparietal GBM (WHO grade IV)	IDH1: unknown MGMT: methylated TERT: unknown 1p/19q: unknown	LEV, LCM
6	45	F	80	Left frontoparietal GBM (WHO grade IV)	IDH1: wild-type MGMT: methylated TERT: mutant 1p/19q: not performed	LZP, TPM
7	39	F	80	Left parietal AA (WHO grade III)	IDH1: mutant MGMT: methylated TERT: wild-type 1p/19q: not performed	LEV, LZP
8	35	M	80	Left frontal ODG (WHO grade II)	IDH1: mutant MGMT: methylated TERT: mutant 1p/19q: co-deleted	LCM, CLZ

Abbreviations: ODG = oligodendroglioma; AA = anaplastic astrocytoma; GBM = glioblastoma; MGMT = O-6-methylguanine-DNA methyltransferase; TERT = telomerase reverse transcriptase; LEV = levetiracetam; DZP = diazepam; LZP = lorazepam; LCM = lacosamide; TPM = topiramate; clonazepam = CLZ.

Table 3
Subject seizure log.

Subject	Seizures in weeks 1–3	Seizures in weeks 4–6	Seizures in weeks 7–9	Seizures in weeks 10–12	Seizures in weeks 13–15	Seizures in weeks 16–18	Mean # of seizures/week
1	1	2	2	1	2	0	0.4706
2	174	99	91	.	.	.	40.4444
3	42	14	35	37	65	51	13.5556
4	1	1	2	3	3	0	0.6250
5	13	0	.	.	.	.	1.7500
6	24	7	4	3	2	0	2.2222
7	1	1	1	1	1	0	0.3125
8	5	2	3	2	2	1	0.9375

O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status had hypermethylation.

The first 4 subjects were treated with a weekly dose escalation. Due to observed fatigue and dizziness, the second 4 subjects had a slower dose increase occurring at 2-week intervals. Only 1 participant completed the entire study as originally planned. Three others also reached a dose of 8 mg/day: 1 participant died due to an unrelated event and 2 other subjects did not tolerate 8 mg/day and required dose reductions. The remaining 4 subjects reached a total dose of 6 mg/day. Additionally, the study was terminated early due to poor accrual.

AEs that were possibly, probably, or definitely attributed to perampanel are listed in Table 2. The most common AEs regardless of the etiology were fatigue (n = 5) and dizziness (n = 2). One participant died 8 weeks after study enrollment secondary to *Pneumocystis jiroveci* pneumonia, which was believed to be unrelated to perampanel. Another participant stopped the study early due to severe fatigue despite reduction in seizures. Perampanel use has been linked to psychiatric side effects, all psychiatric events reported consisted of mild anxiety (n = 1), mild confusion (n = 2), and moderate insomnia (n = 2).

All seizures that occurred on study had focal impaired awareness seizures. Seizure frequency was recorded by subjects for the first 18 weeks of the perampanel administration period as shown in Table 3. Seizure frequencies varied widely between participants. Although, baseline seizure frequencies were not collected, all participants noted ≥3 seizures in one month prior to enrollment with 3 participants having self-reported reductions in seizure frequencies during the trial and 3 additional participants achieving improved seizure control. No participants reached seizure freedom.

This study was encouraging in that 6 out of 8 subjects observed benefit from adjunctive perampanel during the course of this study in reference to seizure reduction. For reference, pooled analysis from 3 large phase III trials demonstrated that 34–53.2% of non-brain tumor patients with focal-onset epilepsy, taking non-enzyme inducing ASDs, had >50% seizure reduction after the addition of perampanel (4 mg–12 mg) [6]. Unfortunately, we could not calculate percent seizure reductions because baseline seizure frequency data was not collected. Other limitations included the small sample size and the degree of subject heterogeneity with respect to glioma subtype and grade, which makes response rates between individuals difficult to compare. Similar to our clinical study, Vecht and colleagues recently reported the results of a prospective study of 12 patients with glioma (WHO grade I–IV) and drug-resistant epilepsy who were treated with perampanel. They showed that perampanel administration at a median dose of 8 mg resulted in 3 subjects experiencing a 50% decrease in seizure activity and an additional 6 subjects achieved complete seizure freedom [7]. Side effects were fairly minimal and similar in nature to what was observed in our study.

It is also noteworthy that a majority of the participants in our study who had a decrease in seizure activity had IDH1 mutant tumors. Due to the high rate of IDH1 mutant tumors within the study population, sampling error cannot be excluded. Nevertheless, this may have clinical relevance as a relationship exists between mutant IDHI and glutamatergic pathways. IDH1 is an enzyme within the citric acid cycle that catalyzes the conversion of isocitrate to α-ketoglutarate. The IDH1 gene is mutated in approximately 70% of grade II/III gliomas and secondary GBMs [8]. The mutated form instead generates 2-hydroxyglutarate (2-HG), which is an oncometabolite and structurally resembles glutamate. One can hypothesize that 2-HG may function as a glutamate receptor agonist. Recently, Chen and colleagues demonstrated that introduction of 2-HG into murine cortical neuronal cell cultures led to increased neuronal electrical activity that was nullified by the application of an *N*-methyl-D-aspartate (NMDA) receptor antagonist [9]. However, this study did not specifically investigate other glutamate receptors, such as AMPA. An earlier experiment involving non-human neuronal cell cultures showed that exogenous 2-HG activated NMDA receptors but did not activate AMPA receptors [10]. To our knowledge, the significance of 2-HG and therefore IDH1 mutations on AMPA receptor signaling in humans is still up for debate [9].

4. Conclusions

In conclusion, this study is consistent with the current literature demonstrating adjunctive perampanel to be a safe option for glioma patients with focal-onset seizures. However, a larger study is recommended to more fully address efficacy within this population. The observation that most responders also had IDH1 mutant tumors raises the possibility that perampanel might be effective in patients whose tumors harbor the mutation due to alterations in glutamatergic pathways. Additional study regarding IDH1/2-HG and AMPA receptor signaling is necessary.

Conflict of interest

Dr. Peters received research funding from Eisai for this study and serves on advisory board for Eisai.

Ethical statement

We have read the Journal's statement regarding ethical publication and affirm that this manuscript is in keeping with those guidelines.

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