Epilepsy Research 145 (2018) 55–62

Contents lists available at ScienceDirect

Epilepsy Research

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

Brivaracetam-induced elevation of carbamazepine epoxide levels: A post-hoc analysis from the clinical development program

Martin J. Brodie[a,*], Toufic Fakhoury[b], Belinda McDonough[c], Anny-Odile Colson[d], Armel Stockis[d], Sami Elmoufti[e], John Whitesides[e]

[a] Epilepsy Unit, West Glasgow ACH-Yorkhill, Glasgow, UK
[b] St. Joseph Health System, Lexington, KY, USA
[c] UCB Pharma, Slough, UK
[d] UCB Pharma, Braine l'Alleud, Belgium
[e] UCB Pharma, Raleigh, NC, USA

ARTICLE INFO

Keywords:
Brivaracetam
Carbamazepine-10,11-epoxide
Epilepsy
Efficacy
Safety

ABSTRACT

To assess the association, if any, between brivaracetam (BRV)-induced elevated carbamazepine-10,11-epoxide (CBZ-E) and toxicity and efficacy in patients with epilepsy. Data were pooled from three double-blind, placebo-controlled, Phase III studies of adjunctive BRV in adults with uncontrolled focal seizures (N01252/NCT00490035, N01253/NCT00464269, N01358/NCT01261325). Treatment-emergent adverse events (TEAEs) of interest (ataxia, diplopia, dizziness, nystagmus, somnolence, accidental overdose or poisoning, and toxicity), discontinuations due to TEAEs, and serious TEAEs (SAEs) were assessed in subgroups who did/did not receive carbamazepine (CBZ) at study entry (CBZ+ and CBZ−). Logistic regression analysis evaluated CBZ-E/CBZ plasma concentrations and TEAEs. SAEs suggestive of CBZ-E toxicity were summarized from the BRV safety database up to a cut-off of October 1, 2014. Percent reduction in focal seizure frequency over placebo was assessed in subgroups of CBZ-E/CBZ ratios. Data from 1558 patients were included in the pooled safety population. Of these, concomitant CBZ was received by 184/459 (40.1%) placebo-treated and 315/803 (39.2%) BRV-treated patients (≥50 mg/day). In BRV-treated patients, study completion rates were similar in the CBZ+ (92.7%) and CBZ− (88.7%) groups; incidence of TEAEs of interest was similar (CBZ+ 24.4%; CBZ− 24.2%), and did not appear affected by CBZ dosage; SAEs and discontinuations due to TEAEs were CBZ+ 1.6%; CBZ− 3.9% and 2.9%; 9.2%, respectively. Likelihood of TEAEs of interest decreased with increasing CBZ-E/CBZ ratio for BRV-treated patients: odds ratio 0.88 (95% confidence intervals 0.74, 1.03; p = 0.112). In the safety database, five SAEs suggestive of CBZ-E toxicity were identified. Efficacy outcomes did not appear to have a consistent pattern across CBZ-E/CBZ ratio subgroups. This post-hoc analysis does not support an association between CBZ-E levels and TEAEs potentially associated with CBZ-E toxicity, or with increases in efficacy. Overall, current evidence does not suggest that BRV dose adjustment is required with concomitant CBZ.

1. Introduction

Brivaracetam (BRV) is a selective, high-affinity ligand for synaptic vesicle protein 2 A (Gillard et al., 2011) which has been approved as adjunctive treatment for focal (partial-onset) seizures in adults with epilepsy. Phase III studies have demonstrated the effectiveness of BRV 50–200 mg/day as an adjunctive treatment for adults and children from 4 years of age with focal seizures (Biton et al., 2014; Klein et al., 2015; Ryvlin et al., 2014).

Carbamazepine (CBZ) is one of the most commonly prescribed antiepileptic drugs (AEDs) worldwide. It was first approved for the treatment of epilepsy in the 1960s, although the proportion of patients with epilepsy treated with CBZ has decreased over time (Hollingworth and Eadie, 2010; Hsieh and Huang, 2011; Landmark et al., 2011; Morales-Plaza and Machado-Alba, 2017; Nicholas et al., 2012). CBZ is extensively metabolized in the liver by cytochrome P450 3A4 (CYP3A4) to form an active metabolite, CBZ-10,11-epoxide (CBZ-E), which is, in turn, metabolized via epoxide hydrolase to an inactive trans-CBZ diol (Novartis, 2015). Despite initial observations more than 30 years ago that CBZ-E could potentially cause toxicity (Patsalos et al., 1985; Pisani et al., 1993; Schoeman et al., 1984; Warner et al., 1992), there is still considerable ambiguity within the literature on this topic (Riva et al.,

* Corresponding author at: Epilepsy Unit, West Glasgow ACH-Yorkhill, Glasgow G3 8SJ, UK.
E-mail address: Martin.Brodie@glasgow.ac.uk (M.J. Brodie).

https://doi.org/10.1016/j.eplepsyres.2018.06.002
Received 22 May 2017; Received in revised form 30 May 2018; Accepted 3 June 2018
Available online 04 June 2018
0920-1211/

1984; Semah et al., 1994; Winnicka et al., 2002) and, therefore, on the clinical significance of elevated CBZ-E levels. Since CBZ-E is thought to be an active metabolite, plasma levels of CBZ-E may be correlated with efficacy (Tomson et al., 1990).

Two Phase I studies have been conducted on concomitant BRV and CBZ exposure, as well as a post-hoc analysis of data from Phase II and Phase III studies. In healthy participants, BRV 400 mg/day (which is above the approved dose range) did not modify exposure to CBZ 600 mg/day (Stockis et al., 2015). In contrast, BRV was associated with a 2.6-fold increase in the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of CBZ-E after 2 weeks of treatment. This increase was shown, in *in vitro* experiments, to arise through a concentration-dependent inhibition of epoxide hydrolase by BRV (Stockis et al., 2015). Similarly, in a pharmacokinetic study in adults with epilepsy, BRV 100–400 mg/day did not modify exposure to CBZ extended-release ≥600 mg/day but resulted in a dose-dependent and reversible increase in CBZ-E, in the presence and absence of valproic acid ≥500 mg/day (Stockis et al., 2016). In a post-hoc analysis of data from five fixed-dose Phase II and III clinical studies in adults with epilepsy, adjunctive BRV 5–200 mg/day did not affect the plasma concentrations of concomitant CBZ, although those of CBZ-E were approximately doubled from geometric mean 1.76 µg/mL without BRV to 3.25 µg/mL at the highest BRV dose of 200 mg/day (Otoul and Stockis, 2015).

To add to the available data on concomitant BRV and CBZ, the objective of this post-hoc analysis was to assess the association, if any, between BRV-induced elevated CBZ-E, and toxicity and efficacy. The analysis may also help address the uncertain clinical significance of elevated CBZ-E levels with regard to both toxicity and efficacy.

2. Material and methods

2.1. Study design

Three double-blind, placebo-controlled, fixed-dose, Phase III studies were conducted to evaluate the efficacy and safety of adjunctive BRV 5–200 mg/day without titration in adults with uncontrolled focal seizures (N01252/NCT00490035 (Ryvlin et al., 2014), N01253/NCT00464269 (Biton et al., 2014), and N01358/NCT01261325 (Klein et al., 2015)). Patients were required to have 1–2 concomitant AEDs, the dose of which was to remain stable throughout the study. The studies were carried out in accordance with International Conference on Harmonization notes for Guidance on Good Clinical Practice and the Declaration of Helsinki (the Code of Ethics of the World Medical Association). Other details of the study designs are summarized in Table 1. Data were pooled from the three Phase III studies for the therapeutic dose range of 50–200 mg/day.

2.2. Blood sampling and bioanalytical determination of plasma AED concentrations

In studies N01252 and N01253, blood sampling for determination of CBZ and CBZ-E plasma concentrations was carried out at Weeks –8, 0, 2, 4, 8, 12, and 15 and early discontinuation visit (EDV). Samples used to determine BRV plasma concentrations were collected at Weeks 0, 2, 4, 8, 12, and EDV. In study N01358, blood sampling for determination of CBZ and CBZ-E plasma concentrations was carried out at Weeks –8, 0, 4, 12, and EDV. Samples for BRV plasma concentrations were collected at Weeks 0, 2, 4, 8, 12, and EDV. Samples were preferably taken immediately prior to the morning dose when the patient was fasting, or at a similar time after dosing on each occasion.

Plasma CBZ, CBZ-E, and BRV concentrations were determined by a liquid chromatography-tandem mass spectrometry method with positive ionization. Waters Oasis HLB solid phase extraction cartridges (Waters Inc, Milford, MA, USA) were conditioned with 500 µL of methanol followed by 500 µL of acetic acid 0.1% (v:v) in H_2O. Following the addition of deuterium-labeled internal standards, aliquots of 50 µL of plasma sample were mixed with 400 µL of acetic acid 0.1% (v:v) in H_2O, transferred to the cartridges, and washed with 500 µL of acetic acid 0.1% (v:v) in H_2O followed by 500 µL of acetic acid 0.1% (v:v) in H_2O:methanol 95:5 (v:v). Samples were eluted with two 500 µL volumes of methanol:H_2O 90:10 (v:v) followed by 500 µL of methanol. After evaporation, samples were reconstituted with 400 µL of methanol:H_2O 25:75 (v:v), and 25 µL aliquots were separated by reverse-phase chromatography using an ACE chromatography C18 column (150*3 mm) (Advanced Chromatography Technologies Ltd, Aberdeen, UK) and analyzed by multiple reaction monitoring detection using a API 3000 mass spectrometer (AB Sciex Llc, Framingham, MA, USA). The assay was validated in the respective quantification ranges [lower–upper limit of quantification (ng/mL)]: CBZ 50 − 5000, CBZ-E 10 − 1000, BRV 5–500. The assay was validated according to Food and Drug Administration and European Medicines Agency guidance.

2.3. Safety and tolerability analyses

Using pooled Phase III data, treatment-emergent adverse events (TEAEs) of interest were summarized for subgroups of patients who were taking concomitant CBZ at study entry (CBZ+) and those who

Table 1
Summary of studies included in the pooled Phase III analysis.

Study number (clinicaltrials.gov identifier)	Treatment period (weeks)	BRV dosages (mg/day)	Inclusion criteria			Exclusion criteria	
			Age (years)	Seizure/ epilepsy type	Number of concomitant AEDs	History/ presence of status epilepticus	Prior AED treatment
N01252 (NCT00490035) (Ryvlin et al., 2014)	12	20, 50, 100	16–70	Focal seizures with/ without secondary generalization	1–2[a]	In the past year	FBM (< 18 months before study) VGB current or past without visual field examination
N01253 (NCT00464269) (Biton et al., 2014)	12	5, 20, 50	16–70	Focal seizures with/ without secondary generalization	1–2[a]	In the past year	FBM (< 18 months before study) VGB current or past without visual field examination
N01358 (NCT01261325) (Klein et al., 2015)	12	100, 200	16–80	Focal seizures with/ without secondary generalization	1–2	In the past year	LEV (current or ≤90 days before study) FBM (< 18 months before study) VGB current or past without visual field examination

AED, antiepileptic drug; BRV, brivaracetam; FBM, felbamate; LEV, levetiracetam; VGB, vigabatrin.
[a] Concomitant LEV limited to 20% of enrolled patients.