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Mini Review

Brivaracetam in epilepsy: A mini-review of the literature

Maria Stefanatou*

1st Department of Neurology, National and Kapodistrian University of Athens, Athens, Greece

***Corresponding author:** Maria Stefanatou, 1st Department of Neurology, National and Kapodistrian University of Athens, Athens, Greece

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Abstract

Brivaracetam (BRV) is the latest approved antiepileptic drug and acts as a high-affinity Synaptic Vesicle protein2A (SV2A) ligand that exceeds the binding potential of Levetiracetam (LEV). In the European Union, BRV is only approved as an adjunctive therapy for the treatment of Partial-Onset Seizures (POS) with or without secondary generalization, in patients 4 years of age and older with epilepsy, while F.D.A. has recently approved its use as monotherapy in partial-onset seizures in adults. In Phase III clinical trials, BRV has shown efficacy and an adequate safety profile in patients suffering from POS. In additional open-label studies, BRV has demonstrated satisfying results and high retention rates in patients with both focal – onset and genetic generalized epilepsies. The main Treatment-Emergent Adverse Events (TEAEs) observed during the regulatory and open label trials were somnolence, dizziness and headache following by fatigue and nausea. Brivaracetam seems to be an effective, easy to use and safe antiepileptic drug in clinical setting.

Introduction

Epilepsy is one of the most common neurologic diseases, affecting over 65 million people worldwide [1]. Despite the expansion of the Antiepileptic-Drug (AED) repertoire, almost one-third of epilepsy patients are reluctant to treatment [2]. Furthermore, many patients suffer from side effects of AEDs, which are responsible for poor adherence and discontinuation of their therapy, resulting to increased risk of uncontrolled seizures and death [3]. Therefore, the research for new AEDs with improved efficacy and safety profiles continues. This article aims at giving a short overview of the recent literature regarding efficacy and tolerability of BRV.

Brivaracetam

Brivaracetam (BRV) is the latest approved antiepileptic drug and acts as a high-affinity synaptic vesicle protein2A (SV2A) ligand that exceeds the binding potential of Levetiracetam (LEV) [4]. In the European Union, BRV is only approved as an adjunctive therapy for the treatment of partial-onset seizures (POS) with or without secondary generalization, in patients 4 years of age and older with epilepsy [5], while F.D.A. has recently approved its use as monotherapy in POS in adults [6]. In Phase III clinical trials, BRV (50–200 mg/day) has shown efficacy and an adequate safety profile in patients suffering from POS [7-9]. In additional open-label studies, BRV has demonstrated satisfying results and high retention rates in patients with both focal – onset and genetic generalized epilepsies [10-12]. The main Treatment-Emergent Adverse Events (TEAEs) observed during the regulatory trials were somnolence, dizziness and headache following by fatigue and nausea [12]. However, results from clinical trials may vary in everyday clinical practice, as these studies have some limitations, as their short duration and strict inclusion /exclusion criteria excludes several subgroups of epilepsy patients. They also follow strict dosage protocols, not allowing any of dosing flexibility [14-16]. Three of these previous randomized, double-blind controlled phase III studies (RCTs) [7-10] (N01252[7] 20/50/100 mg/day; N01253[8] 5/20/50 mg/day; N01358[9] 10/200 mg/day) applied fixed-dose regimens and included only partial-onset epilepsies, whereas one study (N01254[10]) was designed with individual doses (20-150mg/day) and patients with focal (90%) and generalized (10%) epilepsies.

These RCTs recorded 50% responder rates between 32,7 and 55,8% (50mg/day), 36-39% (100%mg/d)and 38% (200mg/day) respectively. In a recent observational study with 156 epilepsy patients, efficacy rates are higher from RCTs with a ≥50% responder rate of 71% (36% seizure-free) at the first follow up visit [17]. 65% of the cohort had already received LEV as antiseizure treatment and 83% of them were on LEV at their baseline visit. The difference in

response in LEV+ and LEV- subgroups was statistically significant. It is well known from previous data [10,14], that previous LEV treatment has been associated with lower BRV efficacy, which could be explained by the similar mechanism of action of the two drugs. However, there are data showing higher ≥50% response rates in patients already administered LEV treatment [13, 17-20]. The two drugs share a similar mechanism of anticonvulsant action, but BRV is a high-affinity synaptic vesicle protein 2A (SV2A) ligand that exceeds the binding potential of LEV by 10 to 30-fold [21], which could explain the high response rates recorded in patients with previous LEV exposure.

In another recent study with a 12-months follow up period, the efficacy of BRV was at the lower end of the effectiveness range [22]. This result may partially be explained by the study protocol, which categorized responders when clinical records only obtained qualitative descriptions of the seizure improvements rather than a specific quantitative measure of frequency reduction. However, retention rate across the whole group was observed to be 87.6% after 3 months, 77.8% after 6 months of FU, and 71.1% at the end of the observation period. Based on 87 patients with N12 months, 25 with N18 months, and 8 patients with N24 months of FU, retention modeling using Kaplan–Meier survival curves predicted that 68.7% of patients would still be taking the medication at 12 months, 64.2% at 18 months, and 59.7% at two years.

There are also additional encouraging data on tolerability and efficacy of BRV in patients with intellectual disability and epilepsy [23]. Seizure frequency reduction and no side effects were reported in more than half of the patients. Retention rates were 84% and 58% on 3rd and 12th month, respectively. It was not recorded significant difference between the LEV + and LEV- subpopulations. In additional data on the BRV's use in different epilepsies [13,22], there are studies showed satisfying outcomes across epilepsy syndromes, providing real life evidence. The molecular similarity to LEV has led towards its use in Genetic Generalized Epilepsy (GGE). In preclinical research, BRV demonstrated suppression of epileptiform activity in genetic absence rat Strasbourg model [24]. In humans with GGE, an essential reduction in photoparoxysmal was recorded after BRV initiation [25].

Regarding its safety profile, BRV seems to be well tolerated with relatively low rate of adverse events (range 14%-39%, with a small proportion of serious TEAEs). In line with RCTs [6-9], in the open label studies [11-14,17-20], the most common side effects were somnolence, dizziness, nausea and behavioral adverse events, such as irritation, aggressiveness and depression. In addition, published data regarding BRV tolerance [12,13,17,26] has shown small proportion of behavioral changes in the switching group from LEV, suggesting that BRV could be an option for patients who have had discontinued LEV due to adverse events. It is known that BRV differs from LEV, as it does not react on α-amino-3-hydroxy-5-methyl-4-isoxazolepropiomic acid (AMPA) receptors [27], whereas LEVE does [28]. The different behavior on AMPA receptors can be an explanation for the different psychotropic effects of the two drugs.

Conclusion

In conclusion, BRV has significant responder rates in different epileptic syndromes. It also seems to have a good safety profile. Therefore, BRV seems to be an effective, easy to use and safe antiepileptic drug in everyday clinical practice.

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