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Research Article

Real-Life Effectiveness and Tolerability of Brivaracetam in Focal to Bilateral and Primary Generalized Tonic-Clonic Seizures

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Purpose. Brivaracetam (BRV), an antiseizure medication indicated for focal-onset seizures, has shown efficacy in the treatment of focal to bilateral tonic-clonic seizures (FBTCS). We aimed to determine the effectiveness and safety of BRV in patients with FBTCS and generalized tonic-clonic seizures (GTCS). *Methods*. We performed a multicenter, retrospective, longitudinal study in adult patients with epilepsy who experienced at least one FBTCS or GTCS before starting BRV (baseline visit). Data were collected from consecutive outpatient visits over a 4-year period. All patients had been followed for at least 3 months before the baseline visit and completed a minimum follow-up of 3 months after starting BRV. Response (≥50% reduction in FBTCS/GTCS frequency) and retention rates, as well as seizure freedom and presence of adverse events at 3, 6, and 12 months, were recorded as outcome measures. *Results*. 114 patients were included (mean age 36.3 ± 18.0 years, 52% male, 36.6% genetic generalized epilepsy); 94 had a 12-month follow-up period. At 12 months' follow-up, the response rate was 83%, and 73.4% of patients were FBTCS/GTCS-free. Retention was 79% at 12 months. Adverse events occurred in 29.8% of patients, the most common being drowsiness (14.9%). No significant differences were found in response rates between FBTCS and GTCS. Drug resistance was independently associated with lower response and seizure freedom rates at follow-up. The absence of a titration period predicted seizure freedom and response at 3 months. *Conclusions*. BRV is an effective and well-tolerated treatment in patients with focal to bilateral tonic-clonic seizures and generalized tonic-clonic seizures.

1. Introduction

A considerable percentage of patients with epilepsy do not achieve seizure freedom with initial antiseizure medications (ASMs) [1, 2]. Bilateral tonic-clonic seizures are associated with higher morbidity and mortality in epilepsy patients [3, 4]; a higher risk of physical injury, traumatic lesions, and sudden unexpected death [4–8]; and poorer quality of life scores [9]. Hence, it is of great clinical interest to control tonic-clonic seizures (both focal to bilateral and primary generalized), to reduce the associated morbidity and mortality.

Brivaracetam (BRV) has been approved as an adjunctive ASM for focal-onset seizures with or without secondary generalization in patients 4 years of age and older [10, 11]. BRV is a synaptic vesicle glycoprotein 2A modulator with high selective affinity, showing 10- to 30-fold greater binding potential than levetiracetam (LEV) [12, 13]. The favorable

safety profile and absence of a titration period have made BRV a promising option in clinical practice [14–17]. The efficacy of this compound in focal to bilateral tonic-clonic seizures (FBTCS) was observed in post hoc analyses of pooled data from phase III trials [18, 19]. In retrospective cohort studies, BRV has shown good response and retention rates in genetic generalized epilepsy syndromes [20–23], although evidence to further support its effectiveness in primary generalized tonic-clonic seizures (GTCS) is still scarce.

We performed a real-life clinical practice study in patients with bilateral tonic-clonic seizures starting treatment with BRV. The aim of the study was to determine the effectiveness and tolerability of BRV in epilepsy patients with FBTCS and GTCS to provide additional evidence for its use in patients with these seizures.

2. Materials and Methods

2.1. Study Design and Participants. This was a multicenter, longitudinal, retrospective observational study including patients ≥ 15 years of age with a definite epilepsy diagnosis and at least one FBTCS or GTCS prior to starting BRV. The study complies with the STROBE guidelines for observational studies and was approved by the local ethics committee (reference number PR(AG)216/2021). Informed consent was obtained at the moment of data collection. Data were collected from outpatient visits covering a period of 4 years (2016 to 2020) in 3 specialized epilepsy units in Spain: Hospital Universitari Vall d'Hebron (Barcelona), Centro de Neurología Avanzada (Seville), and Hospital Universitario Virgen de la Macarena (Seville).

All patients had been evaluated by experienced epileptologists. The epilepsy diagnosis and classification, seizure types, and epilepsy syndrome were defined according to the current International League Against Epilepsy (ILAE) classifications [24–26]. Patients who met the criteria for refractory epilepsy according to the 2010 ILAE Task Force consensus proposal were categorized as drug-resistant [27]. Patients who declined to participate in the study, those without a definite epilepsy diagnosis, those with progressive neurological diseases, and those with any other condition that prevented them from providing reliable seizure diaries were excluded. Patients with incomplete medical records and those lost to follow-up within 3 months after starting BRV were excluded from the analysis.

All consecutive patients with a definite epilepsy diagnosis, at least one previous FBTCS or GTCS, and starting BRV during the set time period were included in the analysis. All patients had been followed for a minimum of 3 months prior to starting BRV. Their demographic data, epilepsy syndrome diagnoses, and previous ASMs were obtained by medical record review.

The baseline visit was defined as the one at which BRV was started. BRV initial maintenance dosage (including titration period when indicated) was established according to the epileptologists' clinical indications at the baseline visit. Data on FBTCS, GTCS, and overall seizure frequency and therapy regimen were collected from the medical records. Indications for starting BRV were lack of efficacy (defined as seizure recurrence after an adequately applied treatment [27]) and/or presence of treatment-emergent adverse events (TEAEs) leading to treatment modification of the previous ASM trial. Baseline seizure frequency was defined as the mean seizure frequency in the 3 months before the baseline visit. At the follow-up visits, patients were reevaluated by an epileptologist, and the following data were collected: BRV dose at each visit, FBTCS, GTCS and overall seizure frequency since last visit, and TEAEs. Seizure frequency was reported by the patients and in seizure diaries. Data regarding treatment retention or withdrawal and concomitant treatment were also collected. All data were extracted retrospectively after completion of the follow-up period by one designated clinical investigator at each center, who was not actively involved in the clinical decisions or the recording of outcome measures in medical records. Data were then collected in a common database specifically designed for the study, ensuring homogeneity of the data. BRV effectiveness was analyzed at 3, 6, and 12 months' follow-up based on the frequency of FBTCS/GTCS during the months between each follow-up visit compared to the frequency in the 3 months before baseline. Patients with a ≥50% reduction in FBTCS or GTCS episodes were considered BRV responders.

2.2. Statistical Analysis. Descriptive and frequency statistical analyses were performed, and comparisons were made using SPSS Statistics 22.0 software. Categorical variables are reported as the frequency (percentage) and continuous variables as the mean ± standard deviation (SD) or the median (interquartile range (IQR)), as appropriate. The normality assumption for quantitative variables was checked with the use of quantile–quantile (Q–Q) plots.

The Wilcoxon signed ranked test was used to assess changes in seizure frequency from the 3 months before baseline to 3, 6, and 12 months of follow-up. Statistical significance in the comparisons with outcome measures was assessed with the Pearson chi-square or Fisher exact test for categorical variables and the Student t test or Mann–Whitney U test for quantitative variables. Multiple logistic regression models were performed to establish independent predictors of response and seizure-free status at each follow-up visit.

Retention rates during follow-up were analyzed with the Kaplan-Meier product limit survival method using the log-rank test to determine statistical significance between groups; retention rates in quantitative variables were assessed with simple Cox proportional hazard models. A multiple Cox regression analysis was performed to obtain predictive factors of treatment discontinuation. A p value <0.05 was considered statistically significant.

3. Results and Discussion

3.1. Demographic and Clinical Characteristics. Among 123 patients recruited, 9 (7.3%) were lost to follow-up, leaving 114 patients included in the final analysis. Mean age was 36.3 ± 18.0 years (range 15-92 years), and 64 patients (52%) were male. Mean age at epilepsy onset was 23.3 ± 20.1 years (range 0-89 years), and 63 patients (51.2%) had

drug-resistant epilepsy. Seventy-eight patients (63.4%) had focal epilepsy, and 45 (36.6%) had genetic generalized epilepsy (formerly known as idiopathic generalized epilepsy). The median baseline frequency of FBTCS/GTCS (during the 3 months before starting BRV) was 0.33 seizures per month (IQR 0-1), and the median overall seizure frequency in this period (including other seizure types) was 1 seizure per month (IQR 0-4). BRV was initiated as an add-on medication in 39 patients (31.7%; first ASM as monotherapy in 1 patient) and as a replacement for another ASM in 84 patients (68.3%; monotherapy in 35). The most commonly replaced ASMs were levetiracetam (50.4%), valproate (4.1%), and perampanel (3.3%). The median BRV dose at baseline was 75 mg/day (IQR 50-100, range: 25-300), and a titration phase was recommended in 44 patients (35.8%). The main indications to start BRV were the presence of TEAEs to prior ASMs (47.2%), lack of efficacy (28.5%), both these indications (20.3%), and other reasons in 4.1%. A detailed summary of the patients' baseline characteristics is shown in Table 1.

A median of 2 (IQR 1-4) ASMs had been discontinued over the patient's history, and the medications most commonly withdrawn were levetiracetam (77.2%), valproate (22.8%), lamotrigine (22%), zonisamide (17.9%), lacosamide (15.4%), carbamazepine (15.4%), eslicarbazepine acetate (14.6%), perampanel (12.2%), and oxcarbazepine (11.4%).

Patients were receiving a median of 1 (IQR 0-2; range 0-4) active ASM at the baseline visit, and 53 (43.2%) were receiving 2 or more concomitant ASMs. The most commonly administered concomitant ASMs were lacosamide (24.4%), eslicarbazepine acetate, and valproate (12.8% each) in focal epilepsy and valproate (44.4%), lamotrigine (26.7%), and clonazepam (17.8%), in generalized epilepsy.

3.2. Effectiveness at Follow-Up. Ninety-seven patients (78.9%) had a 3-month follow-up visit, 104 (84.6%) had a 6-month follow-up visit, and 94 (76.4%) had a 12-month follow-up visit. The median BRV dose at 3 months was higher than that of the baseline visit (100 mg, range 100-200 mg; $p < 0.001$), and it had further increased at 6 months (150 mg, range 100-200 mg; $p = 0.023$). The median dose remained stable at 12 months' follow-up (150 mg, range 100-200 mg; $p = 0.917$).

FBTCS/GTCS frequency was significantly lower at all follow-up time points: response rates were 77.3%, 75%, and 83% at 3, 6, and 12 months, respectively ($p < 0.001$ with respect to baseline). Overall seizure frequency was also significantly lower during follow-up: response rates were 58.8%, 65.4%, and 66% at 3, 6, and 12 months, respectively ($p < 0.001$ with respect to baseline). FBTCS/GTCS freedom rates were 69.1% at 3 months, 68.3% at 6 months, and 73.4% at 12 months. Median freedom rates for all seizure types were 44.3% at 3 months, 50% at 6 months, and 52.1% at 12 months (Table 2 and Figure 1).

At six months' follow-up, older age at epilepsy onset (25.8 vs. 17.1 years; $p = 0.025$), shorter epilepsy duration (11.6 vs. 16.9 years; $p = 0.035$), fewer previous ASMs (median (IQR): 3 [1–5] vs. 5 [3–7]; $p < 0.001$), and lower seizure frequency at baseline (median 0.3 vs. 2.3; $p < 0.001$) were associated with higher response rates in the overall seizure count. Patients with drug-resistant epilepsy were less likely to respond (48.1% vs. 84%; $p < 0.001$). Patients who started BRV as monotherapy (89.7% vs. 56%; $p = 0.001$), as first add-on treatment (91.3% vs. 58%; $p = 0.003$), at higher doses (median 100 vs. 50 mg; $p = 0.005$), or skipped a titration period (77.3% vs. 44.7%; $p < 0.001$) had higher response rates. On multivariate analysis, absence of drug resistance (OR 0.202, 95% CI: 0.078-0.523; $p = 0.001$) and starting BRV at higher doses (OR 1.009 95% CI: 1.001-1.017; $p = 0.036$) were independent predictors of better response rates.

Regarding FBTCS/GTCS, higher 6-month response rates were associated with older age (38.0 vs. 31.3 years; $p = 0.044$), older age at epilepsy onset (25.1 vs. 15.9 years; $p = 0.009$), fewer previous ASMs (median (IQR): 3 [1–5] vs. 5 [4–6]; $p = 0.001$), and lower baseline seizure frequency (median 0.3 vs. 0.7; $p = 0.002$). Patients with drug-resistant epilepsy showed a smaller 6-month response for these seizures (59.3% vs. 92%, $p < 0.001$), whereas those who started BRV as monotherapy (93.1% vs. 68%; $p = 0.008$), as first add-on treatment (91.3% vs. 70.4%; $p = 0.041$), and skipping the titration period (83.3% vs. 60.5%, $p = 0.010$) had a greater 6-month response. On multivariate analysis, drug resistance was the only independent predictor of lower response rates for tonic-clonic seizures (OR: 0.126, 95% CI 0.040-0.402; $p < 0.001$) (Table 3).

An older age at diagnosis (27.3 vs. 18.3 years; $p = 0.016$), shorter epilepsy duration (10.7 vs. 16.2 years; $p = 0.019$), previous use of fewer ASMs (median (IQR): 2 [1–3] vs. 5 [3–7], $p < 0.001$), and lower baseline monthly seizure frequency (median 0.3 vs. 3.5; $p < 0.001$) were associated with higher all seizure freedom rates. A smaller percentage of patients with drug-resistant epilepsy were all seizure-free at 6 months (24.1% vs. 78%; $p < 0.001$). Patients who started BRV as monotherapy (82.8% vs. 37.3%; $p < 0.001$), as first add-on therapy (87% vs. 39.5%; $p < 0.001$), without a titration period (63.6% vs. 26.3%; $p < 0.001$), and at a higher initial dose (median 100 vs. 50 mg/day; $p = 0.001$) were more likely to remain seizure-free at 6 months' follow-up. On multivariate analysis, fewer ASMs prior to starting BRV (OR 0.750, 95% CI: 0.576-0.976; $p = 0.032$), drug-responsive epilepsy (OR 0.212, 95% CI: 0.067-0.671; $p = 0.008$), and higher BRV starting doses (OR 1.008 95% CI: 1.000-1.016; $p = 0.047$) were independent predictors of higher 6-month seizure freedom rates.

The clinical factors associated with higher seizure freedom rates at 6 months included older age (38.7 vs. 31.2 years; $p = 0.017$), older age at epilepsy onset (25.9 vs. 16.1 years; $p = 0.003$), focal epilepsy (75.4% vs. 56.4%, $p = 0.044$), lower monthly tonic-clonic seizure frequency at baseline (median 0 vs. 1, $p < 0.001$), and fewer previous ASMs (median (IQR): 3 (1-4.5) vs. 5 [4–6], $p < 0.001$). Patients with drug-resistant epilepsy were less seizure-free (50% vs. 88%, $p < 0.001$). Patients who started BRV as monotherapy (89.7% vs. 60%, $p = 0.004$), as first add-on therapy (87% vs. 63%, $p = 0.029$), and without a titration period (77.3% vs 52.6%, $p = 0.009$) were more likely to remain seizure-free. On multivariate analysis, absence of drug resistance was independently associated with seizure freedom at 6 months (OR: 0.136 95% CI 0.050-0.373; $p < 0.001$) (Table 3).

Table 1: Demographic and clinical characteristics and BRV initiation at baseline visit.

	$N = 123$
Male sex, *n* (%)	64 (52.0)
Age, years, mean ± SD (range)	36.3 ± 18.0 (15-92)
Age at onset, mean ± SD (range)	23.3 ± 20.1 (0-89)
Age at onset, *n* (%)	
<5 years	15 (12.2)
5-11 years	22 (17.9)
12-20 years	42 (34.1)
21-45 years	23 (18.7)
46-59 years	13 (10.6)
≥60 years	8 (6.5)
Epilepsy duration, years, mean ± SD (range)	13.0 ± 11.8 (0-59)
Type of epilepsy, *n* (%)	
Focal	78 (63.4)
Generalized	45 (36.6)
Epilepsy syndrome and etiology, *n* (%)	
Focal epilepsy	78 (63.4)
Unknown etiology	28 (22.8)
Structural etiology	50 (40.7)
Genetic generalized epilepsy	45 (36.6)
Other	2 (1.6)
Juvenile myoclonic epilepsy	8 (6.5)
GGE with GTCS	32 (26.0)
Juvenile absence epilepsy	2 (1.6)
Childhood absence epilepsy	1 (0.8)
Drug-resistant epilepsy, *n* (%)	63 (51.2)
Tonic-clonic seizure types, *n* (%)	
GTCS	45 (36.6)
FBTCS	78 (63.4)
Number of FBGTS/GTCS in the 3 months prior to inclusion (median)	1 (IQR: 0-3) (range: 0-30)
Monthly FBTCS/GTCS frequency	0.33 (IQR: 0-1) (range: 0-10)
Number of FBTCS/GTCS in the last year prior to inclusion (median)	2 (IQR: 0-6) (range: 0-120)
Monthly FBTCS/GTCS frequency	0.17 (IQR: 0-0.5) (range: 0-10)
Other seizure types in the 3 months prior to inclusion, *n* (%)	70 (56.9)
Focal seizures without impaired awareness	9 (7.3)
Focal seizures with impaired awareness	37 (30.1)
Myoclonic	17 (13.8)
Absences	15 (12.2)
Other	8 (6.5)
Median seizure frequency per month in the 3 months prior to inclusion (all seizure types)	1 (IQR: 0-4) (range: 0-64)
Median seizure frequency per month in 1 year prior to inclusion (all seizure types)	0.5 (IQR: 0.1-2.7) (range: 0-42)
BRV dose (mg)	75 (IQR:50-100) (range:25-300)
Titration phase, *n* (%)	44 (35.8)

BRV: brivaracetam; FBTCS: focal or bilateral tonic-clonic seizures; GGE: genetic generalized epilepsy; GTCS: generalized tonic-clonic seizures; SD: standard deviation.

Twenty-three patients discontinued BRV at some point during follow-up. Retention rates were 92.3%, 88%, and 79% at 3, 6, and 12 months, respectively, with a median dose at withdrawal of 150 mg/day. The main reasons for withdrawal were lack of efficacy in 13 patients (48.1%), TEAEs in 9 (33.3%), both in 2 (7.4%), and other reasons in 3 patients (11.1%). None of the clinical factors were statistically associated with a higher probability of withdrawal, although there was a trend toward a lower retention rate in patients with generalized epilepsy than in those with focal

Table 2: Seizure frequency and response rates at follow-up.

	Baseline ($n = 123$)	3 months ($n = 97$)	6 months ($n = 104$)	12 months ($n = 94$)
BRV dose, median (IQR)	75 (50-100)	100 (100-200)	150 (100-200)	150 (100-200)
FBTCS/GTCS				
Monthly seizures, median (IQR)	0.3 (0-1)	0 (0-0.3)	0 (0-0.9)	0 (0-0.1)
Seizure-free, *n* (%)	50 (40.7)	67 (69.1)	71 (68.3)	69 (73.4)
Response rate, *n* (%)	—	75 (77.3)	78 (75)	78 (83)
All seizures				
Seizures/month, median (IQR)	1 (0-4.3)	0.3 (0-3.3)	0.1 (0-2)	0 (0-1.7)
Seizure-free, *n* (%)	27 (22)	43 (44.3)	52 (50)	49 (52.1)
Response rate, *n* (%)	—	57 (58.8)	68 (65.4)	62 (66.0)

BRV: brivaracetam; FBTCS/GTCS: focal to bilateral tonic-clonic seizures/generalized tonic-clonic seizures; IQR: interquartile range.

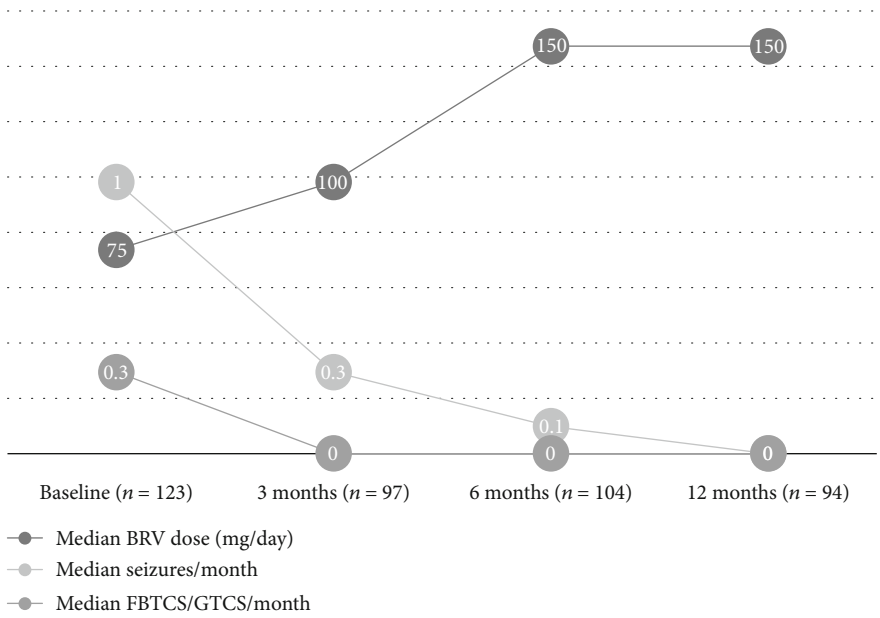

Figure 1: Brivaracetam dose and seizure frequency at follow-up. The figure shows increasing doses in the first 3 to 6 months of treatment, with stabilization at 6-12 months. Median seizure frequency (both FBTCS/GTCS and overall seizures) is seen to decrease since the baseline visit. FBTCS/GTCS remain near 0 after 3 months of treatment. BRV: brivaracetam; FBTCS/GTCS: focal to bilateral tonic-clonic seizures/generalized tonic-clonic seizures.

epilepsy (72.7% vs. 83.2%; $p = 0.058$), or higher baseline seizure frequency vs. lower (1.3 vs. 0.8; $p = 0.060$).

3.3. Treatment-Emergent Adverse Events. During the overall follow-up period, 34 patients (29.8%) reported a total of 52 TEAEs (20.6%, 14.4%, and 10.6% at 3, 6, and 12 months, respectively). The most commonly reported TEAEs were drowsiness (14.9%), irritability (4.4%), dizziness (1.8%), and weight gain (1.8%). A summary of the specific TEAEs that occurred is provided in Table 4. No clinical factors were associated with higher TEAE rates.

3.4. Generalized Epilepsy Compared to Focal Epilepsy. A comparison was performed between patients with a diagnosis of focal ($n = 78$) or generalized ($n = 45$) epilepsy at baseline. Patients with generalized epilepsy were younger (mean age 27.5 ± 10.8 y vs. 41.4 ± 19.3 y; $p < 0.001$), had a lower mean age at epilepsy onset (15.8 ± 9.1 years vs. 27.7 ± 23.2 years; $p < 0.001$), and included a larger percentage of females (62.2% vs. 39.7%; $p = 0.016$). There were no differences in terms of epilepsy duration or drug resistance. Patients with generalized epilepsy had a higher monthly frequency of GTCS in the 3 months before baseline than those with focal epilepsy (median 0.7 (IQR 0.3-1.2) vs. 0 (IQR 0-0.7); $p < 0.001$), but there were no significant differences in the overall seizure frequency relative to baseline between the two groups. Patients with generalized epilepsy had received a larger number of previous ASMs (median 3 (IQR 1-4) vs. 1 (IQR 1-3); $p = 0.028$). There were no significant differences between the groups regarding BRV dose, titration, indication for starting the treatment, or the form of administration (as add-on therapy or monotherapy).

At the follow-up visits, there were no significant differences in response and overall seizure freedom rates between

Table 3: Clinical and treatment-related factors associated with response and seizure freedom rates for FBTCS/GTCS during follow-up.

	3 months				6 months				12 months			
	Seizure-free		Responder		Seizure-free		Responder		Seizure-free		Responder	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Univariate analysis												
Sex, male	43.3%	52.2%	36.4%	53.3%	51.5%	49.3%	53.8%	48.7%	32%*	55.1%*	31.3%	52.6%
Age	31.9	37.4	34.9	35.9	31.2*	38.7*	31.3*	38*	28*	37.5*	25.4*	37.0*
Age at onset, years, mean	15.4*	24.5*	16.1	23.3	16.1*	25.9*	15.9*	25.1*	13.6*	25.6*	12.4*	24.5*
Epilepsy duration, years, mean	16.8	12.9	18.4	12.8	15.0	12.7	15.3	12.8	13.9	12.0	13	12.4
Type of epilepsy, focal	46.7%*	68.7%*	54.5%	64%	48.5%*	69%*	53.8%	65.4%	44%*	66.7%*	56.3%	61.5%
Drug-resistant epilepsy	80%*	41.8%*	72.7%*	48%*	81.8%*	38%*	84.6%*	41.0%*	84%*	42%*	81.3%*	47.4%*
Number of previous ASMs, median	5*	3*	5*	3*	5*	3*	5*	3*	5*	3*	5	3
BRV dose, mg, median	50	100	50	100	50	100	50	100	50	100	50	100
Titration	63.3%*	25.4%*	63.6%*	29.3%*	54.5%*	28.2%*	57.7%*	29.5%*	56%*	26.1%*	50%	30.8%
Monotherapy	10%*	32.8%*	13.6%	29.3%	9.1%*	36.3%*	7.7%*	34.6%*	4%*	37.7%*	6.3%*	33.3%*
First add-on	3.3%*	25.4%*	4.5%	22.7%	9.1%*	28.2%*	7.7%*	26.9%*	12%	27.5%	18.8%	24.4%
Multivariate analysis												
Sex, male	—		—		—		—		$p = 0.044$		—	
Focal epilepsy	$p = 0.022$		—		—		—		—		—	
Drug-resistant epilepsy	—		—		$p < 0.001$		$p < 0.001$		$p = 0.001$		$p = 0.021$	
No titration period	$p < 0.001$		$p = 0.005$		—		—		—		—	

*p value < 0.05. ASMs: antiseizure medications; BRV: brivaracetam; FBTCS/GTCS: focal to bilateral tonic-clonic seizures/generalized tonic-clonic seizures.

Table 4: Treatment-emergent adverse events during follow-up.

	3 months ($n = 97$)	6 months ($n = 104$)	12 months ($n = 94$)	Total ($n = 114$)
Patients reporting TEAEs, *n* (%)	20 (20.6)	12 (14.4)	10 (10.6)	34 (29.8)
Total number of different TEAEs	30	16	15	52
Reported symptoms, n (%)				
Ataxia	—	—	1 (1.1)	1 (0.9)
Weight gain	—	1 (1)	1 (1.1)	2 (1.8)
Weakness	1 (1)	—	1 (1.1)	1 (0.4)
Drowsiness	10 (10.3)	6 (5.8)	3 (3.2)	17 (14.9)
Dizziness	1 (1)	—	1 (1.1)	2 (1.8)
Irritability	4 (4.1)	—	2 (2.1)	5 (4.4)
Other	9 (9.3)	8 (7.7)	6 (6.4)	16 (14)

TEAEs: treatment-emergent adverse events.

patients with focal or generalized epilepsy. However, patients with focal epilepsy had higher freedom rates from tonic-clonic seizures at 3 (76.7% vs. 56.8%; $p = 0.039$), 6 (75.4% vs. 56.4%; $p = 0.044$), and 12 months (80.7% vs. 62.2%; $p = 0.047$) (Figure 2).

Compared to patients with focal epilepsy, those with generalized epilepsy showed a trend toward a lower retention rate at 12 months' follow-up (72.7% vs. 83.2%, $p = 0.058$). There were no significant differences in the reasons for BRV withdrawal or presence of adverse events between the two groups.

4. Discussion

This study describes the results of real-life BRV use in a representative sample of patients with generalized convulsive seizures (focal or generalized epilepsy) and a minimum follow-up of three months. In line with previous studies, our results show response rates of around 60% in the overall seizure count during follow-up, and more than 75% in FBTCS/GTCS [28, 18, 19, 29], with no differences between patients with focal or generalized epilepsy. These results support the potential usefulness of BRV for fast, optimized seizure control.

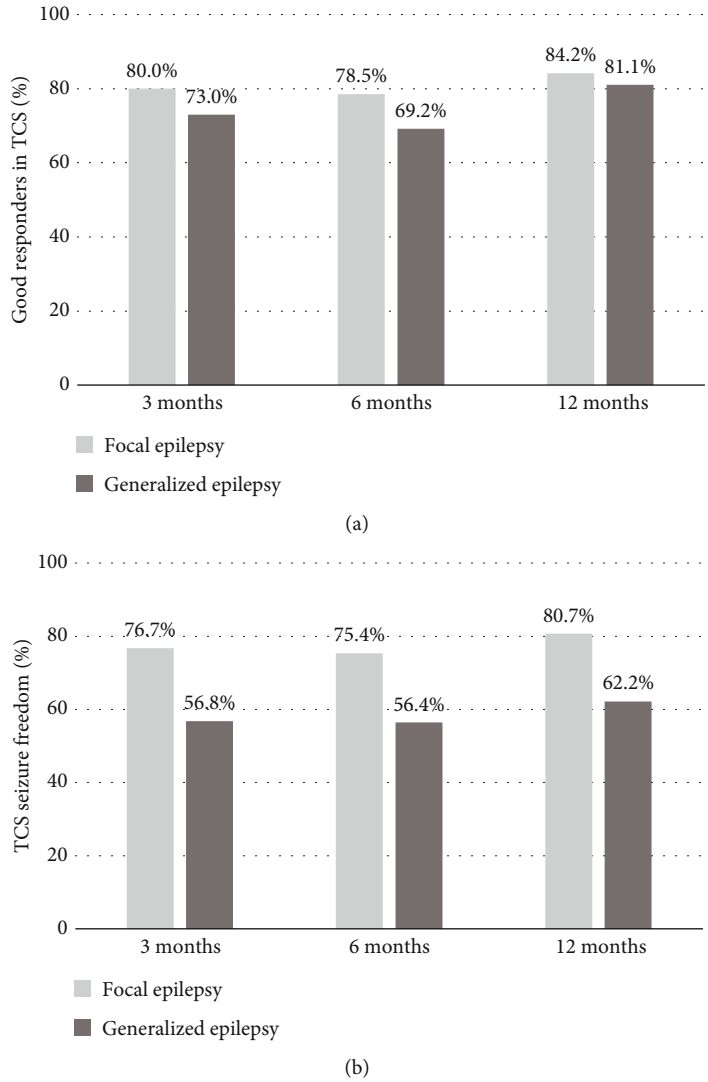

Figure 2: Response (a) and tonic-clonic seizure freedom (b) rates in patients with focal or generalized epilepsy. Similar response rates were observed in the two groups at 3-, 6-, and 12-month follow-ups, whereas tonic-clonic seizure freedom rates were higher in patients with focal epilepsy. Tonic-clonic seizure freedom rates above 55% were seen in both groups throughout follow-up. TCS: tonic-clonic seizures.

The starting BRV dose in our sample was similar to those described in previous postcommercialization studies [29, 30], and doses remained stable during follow-up. Our sample includes patients who received high doses of BRV, mostly due to the proportion of drug-resistant patients included. Overall, a higher starting BRV dose was independently associated with higher response rates and seizure freedom. In addition, most patients skipped the titration phase, and this was independently associated with a response against tonic-clonic seizures at 3 months' follow-up. These findings support previous reports suggesting that therapeutic doses should be started from the first day to quickly achieve seizure control without increasing the risk of TEAEs [15, 31]. This is particularly relevant in the case of tonic-clonic seizures, which carry a higher risk of injuries and unexpected sudden death. However, in our study, a titration phase was still considered in some patients at clinicians' criteria, mostly in those patients with high ASM overload and those with a previous history of TEAEs with other ASMs, and therefore, no definite conclusions can be reached regarding this matter from our results.

A large percentage of patients with drug-resistant epilepsy used BRV in combination with other ASMs. As would be expected, drug resistance was the main clinical factor independently associated with lower response and seizure freedom rates [32]. However, half the patients with drug-resistant epilepsy were free of tonic-clonic seizures during follow-up, and up to 24% were free of all seizures. These results uphold the potential benefit of this treatment even in patients with refractory epilepsy and failure to several ASMs [33, 34].

The retention rate in our sample was similar to values reported in previous series but was slightly higher than those described in previous postcommercialization studies having longer follow-up periods [19, 23, 29, 35, 36]. This difference could be attributable to the shorter follow-up of

our study, which was mainly focused on the first months after starting treatment.

Similar to the findings in postcommercialization studies, adverse events occurred in almost 30% of our patients, and in most cases, they were mild and did not lead to treatment discontinuation. Nonetheless, TEAEs were the main reason for discontinuation, as has been reported [23, 34–36]. Some clinical trials have described higher TEAE [16, 19], but they were mainly considered mild and did not require treatment discontinuation. The retrospective design of most postcommercialization studies may have underestimated adverse events of less clinical relevance.

Our study included patients with genetic generalized epilepsy in which BRV was initiated off-label. The frequency of GTCSs and the number of previous ASMs were higher in these patients at baseline. This likely represents a selection bias, as this is a more difficult-to-treat patient population, especially in women of childbearing potential in whom avoiding valproate may have influenced baseline seizure control. Accordingly, this group of patients had lower seizure freedom rates during follow-up compared to patients with focal epilepsy. However, overall seizure freedom rates were above 55% both in patients with GTCS and those with FBTCS throughout the follow-up. The effectiveness results provide further evidence of the potential benefit of BRV in tonic-clonic seizures, whether patients have a focal or generalized epilepsy type [28, 11, 20, 23].

The retrospective design, wide age range, and high percentage of drug-resistant patients, as well as the differing epilepsy syndromes and etiologies of the patients included, are some of the main limitations of this study. The retrospective design might have also introduced a selection bias in those cases in which reliable seizure frequency could not be obtained or those with progressive conditions. In addition, the short follow-up period may have overestimated some outcome measures such as seizure frequency and retention rates, whereas some TEAEs may have been underrepresented. Also, the observational design did not allow to control some confounding factors and cointerventions such as other ASM modifications during follow-up. Nevertheless, the results provide real-life data regarding the usefulness of BRV to control FBTCS/GTCS in focal and generalized epilepsies. Larger prospective, randomized, placebo-controlled trials with longer follow-up periods are needed to confirm these results.

5. Conclusions

Brivaracetam is an effective and well-tolerated ASM in patients with focal or generalized epilepsy experiencing bilateral tonic-clonic seizures. As the therapeutic effect can be achieved from the first day of treatment, brivaracetam can be considered a promising option to avoid the complications associated with these seizures.

Data Availability

After publication, anonymized data supporting the findings of this study will be available from the corresponding author upon reasonable request from any qualified investigator.

Disclosure

The funder was involved in the study design, follow-up, data evaluation, and analysis and writing process.

Conflicts of Interest

E. Fonseca declares research funding and honoraria from UCB Pharma, Esteve Laboratorios, Eisai Inc., Bial Pharmaceutical, GW Pharmaceuticals, Angelini Pharma, and Sanofi Genzyme. A. Gifreu declares research funding from UCB Pharma and Bial Pharmaceutical. Manuel Quintana has received honoraria from UCB Pharma, Eisai Inc., Sanofi, GW Pharmaceuticals, Neuraxpharm Spain, and Pierre Fabre Ibérica. S. Lallana has received travel support and research funding from UCB Pharma and Bial Pharmaceutical. S. López-Maza declares travel support and research funding from Eisai Inc., UCB Pharma, and Neuraxpharm Spain. L. Abraira has received research funding and speaker fees from UCB Pharma, Bial Pharmaceutical, Eisai Inc., Sanofi Genzyme, and Esteve Laboratorios. D. Campos-Fernández has received research funding from UCB Pharma. E. Santamarina has received research funding and speaker fees from UCB Pharma, Bial Pharmaceutical, Eisai Inc., Arvelle, and Esteve Laboratorios. J. Rodríguez Uranga declares honoraria from Arvelle, Angelini Pharma, Bial Pharmaceutical, Eisai Inc., Esteve Laboratorios, UCB Pharma, and Pfizer Inc. M. Toledo declares research funding and speaker fees from UCB Pharma, GW Pharmaceuticals, Bial Pharmaceutical, Eisai Inc., Sanofi, Arvelle, and Esteve Laboratorios. J Abril Jaramillo and L. Redondo Vergé have no conflict of interest to declare.

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