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Intravenous brivaracetam in status epilepticus: A multicentric retrospective study in Italy

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ABSTRACT

Purpose: to evaluate the use, effectiveness, and adverse events of intravenous brivaracetam (BRV) in status epilepticus (SE).

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Treatment
Efficacy

Methods: a retrospective multicentric study involving 24 Italian neurology units was performed from March 2018 to June 2020. A shared case report form was used across participating centres to limit biases of retrospective data collection. Diagnosis and classification of SE followed the 2015 ILAE proposal. We considered a trial with BRV a success when it was the last administered drug prior the clinical and/or EEG resolution of seizures, and the SE did not recur during hospital observation. In addition, we considered cases with early response, defined as SE resolved within 6 h after BRV administration.
Results: 56 patients were included (mean age 62 years; 57 % male). A previous diagnosis of epilepsy was present in 21 (38 %). Regarding SE etiology classification 46 % were acute symptomatic, 18 % remote and 16 % progressive symptomatic. SE episodes with prominent motor features were the majority (80 %). BRV was administered as first drug after benzodiazepine failure in 21 % episodes, while it was used as the second or the third (or more) drug in the 38 % and 38 % of episodes respectively. The median loading dose was 100 mg (range 50−300 mg). BRV was effective in 32 cases (57 %). An early response was documented in 22 patients (39 % of the whole sample). The use of the BRV within 6 h from SE onset was independently associated to an early SE resolution (OR 32; 95 % CI 3.39–202; $p = 0.002$). No severe treatment emergent adverse events were observed.
Conclusion: BRV proved to be useful and safe for the treatment of SE. Time to seizures resolution appears shorter when it is administered in the early phases of SE.

1. Introduction

Brivaracetam (BRV) is a high-affinity synaptic vesicle glycoprotein 2A ligand (SV2A) that is currently licensed as monotherapy or adjunctive therapy for the treatment of focal-onset seizures in people with epilepsy aged ≥ 4 years [1]. After oral administration, BRV is rapidly and completely absorbed; it has low (< 20 %) plasma protein binding and a linear and predictable pharmacokinetic profile [2]; furthermore, it carries low risks of drug–drug interactions [3]. Recently, BRV has gained interest for its use in emergency situation such as acute repetitive seizure and status epilepticus (SE). BRV has several characteristics that could be useful in these conditions. When compared to levetiracetam (LEV), affinity of BRV to SV2A is stronger both in animal models of epilepsy and in human brains [4]. In addition, BRV is more lipophilic, thus it crosses the blood-brain barrier more rapidly than levetiracetam (LEV). Nicolas et al. described physiologically-based pharmacokinetic models that showed how intravenous (IV) administration of a single dose of BRV reaches the central nervous system within a few minutes in humans, compared to an hour for LEV [5].

Status epilepticus (SE) is a life-threatening condition and a medical emergency associated with long-term consequences, including "neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures" [6] and it carries a risk of mortality around 20 % [7] increasing up to 33 % in patients with impaired consciousness [8]. The pharmacological management of SE follows a stepwise approach. Fast-acting benzodiazepines (BDZ) are administered as first-line treatment, leading to SE cessation in about 60 % of cases [9]. In benzodiazepine-resistant cases, IV administration of anti-seizures medications (ASMs) is required to control SE and prevent or minimize the risk of negative long-term systemic or neuronal consequences [9,10].

Although BRV is currently not labelled to treat SE, preclinical studies have been encouraging and showed efficacy in animal models of SE [11, 12]. Moreover, preliminary clinical real-world data have been reported by different authors. Four series of patients with SE treated with BRV have been published to date. The Strzelczyk et al. series [13] consisted of 11 patients with refractory SE, with a response rate of 27 %; Kalss et al. [14] reported a higher effectiveness rate of 57 % in seven patients who received BRV in an earlier phase; Aicua-Rapun et al. reported a series of 14 patients with a SE control rate of 50 % [15]. Finally, the series from Santamarina et al. [16] described IV BRV used in 43 patients with an overall effectiveness of 54 % and response rate that seemed higher when BRV was administered earlier and at higher doses.

On the basis on these data, our aim was to assess the use of IV BRV in a larger cohort of patients with SE, to define the effectiveness and safety of its use.

2. Methods

2.1. Study design and participants

This was a retrospective, observational, multicenter study on patients with SE who were treated with IV BRV. This study involved 24 Italian neurology units. The data were collected from March 2018 to June 2020. No SE etiology was excluded. The numbers of patients provided by the participating hospitals are reported in **Supplementary** Table 1. A shared case report form was used across participating centres to limit biases of retrospective data collection.

Status epilepticus was defined as a continuous seizure or two or more discrete seizures between which there is no complete recovery of consciousness that lasts ≥ 5 min for convulsive SE (CSE) [6]. In cases of Non-Convulsive Status Epilepticus (NCSE), which means a SE episode not accompanied by prominent motor phenomena or with subtle motor phenomena, a 10-minutes cut-off time was adopted [6]. In all these cases the diagnosis of NCSE was confirmed by reviewing centrally native EEG and cases according to Salzburg EEG criteria by authors NO, SM and GG [17,18].

The variables recorded included demographic profile data (gender, age) and a prior history of seizures or epilepsy. With regard to SE, the latest classification proposed by

the International League Against Epilepsy (ILAE) [6] was followed: patients with prominent motor symptoms included generalized convulsive, myoclonic, or focal motor SE, while SE without prominent motor symptoms (not convulsive) included patients in coma and focal seizures with and without impaired consciousness. The etiology of the SE was determined based on the ILAE classification (acute symptomatic, remote symptomatic, progressive symptomatic, or unknown). Moreover, SE was classified as multifactorial when more than one of the aforementioned categories were simultaneously present and judged equally important in SE determination.

According to treatment outcomes, established status epilepticus (ESE) was defined as a SE without clinical and/or electroencephalographic resolution after the administration of first line agents (benzodiazepines). Refractory status epilepticus (RSE) was defined as a SE that persists, regardless of the delay since the onset of the seizure, after failure of a trial of at least one ASM, at adequate dosage, requiring consequently the use of anesthetic drugs.

To assess the short-term prognosis of SE, the STESS (Status Epilepticus Severity Score) [19] and EMSE (Epidemiology based Mortality score in Status Epilepticus) [20,21], were calculated for every patient at baseline.

All the lines of treatment and the number of ASMs used were collected, as well as the need to administer IV anesthetic drugs. For BRV, data were gathered concerning the order in which it was used, the time from SE onset to BRV use, the total loading dose, the weight-adjusted

loading dose and the maintenance dose.

2.2. Study outcomes

We considered a trial with BRV successful in terminating SE (effectiveness), when it was: (1) the last drug administered within 72 -h prior the clinical and/or EEG resolution of SE, without other changes in the concomitant medication, and (2) the SE didn't recur during the entire hospital observation of the patient [10,22]. Moreover, to limit biases related to the retrospective data collection, we gathered data also on a more restrictive definition of effectiveness considering the SE episodes resolved within 6 h from IV BRV. We added this second definition of effectiveness because in the context of SE it has a high clinical relevance to obtain a fast and early response to IV ASMs. [16].

For SE episodes with multiple ASMs trials treatment schedules for dose adjustment of concomitant medication were reviewed.

Secondary outcomes were the incidence and features of adverse events observed for BRV. We classified an event as 'adverse event' if appeared in close temporal relationship with the administration of BRV and if it is reported in the safety profile of the drug.

The response to treatment was monitored clinically and with EEG to verify the disappearance of continuous epileptic activity. EEG monitoring was performed at intervals in the majority of the cases, as continuous EEG was not available at most centers.

2.3. Standard protocol approvals and data availability

The scientific advisory board of our Institution approved the research protocol according to local regulations and the local Ethic Committee approved the retrospective analysis of patients' data. This study is a retrospective documentation of individual treatment decisions without research approach in an emergency setting.

The authors state that the anonymized data on which the article is based will be shared by request of any qualified investigator.

2.4. Statistical analysis

Variables are presented as absolute number and percentage, median (range) or mean (± standard deviation, SD). Categorial variables were analyzed with X^2 or Fischer's exact test whereas continuous variables were analyzed using the independent samples T-test or the Mann–Whitney U-test, as appropriate. To assess independent predictors of BRV response, we implemented baseline characteristics associated with a $p < 0.05$ in the univariate analysis and those judged clinically relevant into multivariate binary logistic regression model. A p value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows, version 21 (SPSS Inc., Chicago, IL, USA).

3. Results

In the study period 59 patients were initially enrolled but after central review of each single case, three patients were discarded due to limited information. Therefore, 56 subjects were included in the analysis (Table 1). The mean age was 61.2 ± 19.1 years, 57 % (n = 32) were male and 38 % (n = 21) had a history of epilepsy. With regard to etiology, half of the cohort had a SE that was considered to be acute symptomatic (n = 26, 46 %). BRV was used in two episodes of post-anoxic SE. Only in one patient BRV was used in the context of a generalized genetic epilepsy (GGE; juvenile absence epilepsy). As far as semiology is concerned, 80 % (n = 45) had SE with prominent motor symptoms at presentation. In 27 of these patients (48 %) the SE evolved into a NCSE, while the 20 % of SE (n = 11) was non-convulsive from onset.

BRV use, effectiveness and clinical outcomes are reported in Table 2. In 12 cases BRV was used as first ASM after BDZ failure (21 %) and in two occasions it was used as first treatment line, instead of BDZ. BRV was used after the failure of a benzodiazepine (BDZ) plus another ASM in 21 cases (38 %), and as third or more ASM in another 21 SE episodes (38 %). The time from SE diagnosis to BRV administration was from less than 1 h to 18 days (median 48 h). The median loading dose was 100 mg (range 50–250 mg) with a mean weight-adjusted loading dose of 1.34 mg/kg (0.53–2.94). Time of bolus dose's infusion was around 10−15 min in every case, but in three cases a fast bolus in 3-minutes was used.

Table 1
Baseline characteristics of the sample of SE patients treated with brivaracetam (n = 56 patients).

Characteristic/variable	Value
Age, mean ± SD, y	61.9 ± 19.1
Gender, male, n (%)	32 (57 %)
Previous Epilepsy, n (%)	21 (38 %)
Etiology classification	
Acute symptomatic, n (%)	26 (46 %)
Remote symptomatic, n (%)	10 (18 %)
Progressive symptomatic, n (%)	9 (16 %)
Cryptogenic, n (%)	2 (4%)
Multifactorial, n (%)	6 (10 %)
Post-anoxic SE, n (%)	2 (4%)
SE in GGE, n (%)	1 (2%)
Semeiology classification	
With prominent motor symptoms, n (%)	45 (80 %)
Convulsive, n (%)	6 (10 %)
Focal motor, n (%)	11 (20 %)
Myoclonic, n (%)	1 (2%)
Motor with evolution in NCSE, n (%)	27 (48 %)
Without prominent motor symptoms (NCSE), n (%)	11 (20 %)
Prognostic scores	
STESS, median	3
EMSE, median (range)	77.5 (3–153)

Abbreviations: BRV, brivaracetam; GGE, genetic generalized epilepsy; LEV, levetiracetam; NCSE, non-convulsive status epilepticus; SD, standard deviation; SE, status epilepticus; STESS, Status Epilepticus Severity Score; EMSE, Epidemiology based Mortality score in Status Epilepticus.

Table 2
Brivaracetam use, effectiveness, and clinical outcomes (n = 56 patients).

Characteristic/variable	Value
Patients with refractory SE at BRV use, n (%)	36 (64 %)
Time from SE diagnosis to BRV use, hours, median (range)	48 (0.8–432)
Loading dose of BRV, median, mg (range)	100 (50–250)
Loading dose of BRV adjusted by weight, mg/kg	Mean 1.34 Median 1.33 Range 0.5–2.9
BRV used instead of BDZ, n (%)	2 (4%)
Order of treatment with BRV (after BDZ)	
First, n (%)	12 (21 %)
Second, n (%)	21 (38 %)
Third (or more), n (%)	21 (38 %)
LEV used prior to BRV, n (%)	15 (27 %)
SE resolved after BRV (effectiveness), n (%)	32 (57 %)
Time to SE cessation, hours, median (range)	3 (0.08–72)
SE resolved < 6 h after BRV, n (%)	22 (39 %)
Treatment-emergent adverse events, n (%)	6 (12 %), 5 somnolence, 1 transient increase of liver enzymes
Withdrawal due to adverse events, n (%)	0
Death at discharge, n (%)	15 (27 %)
BRV at discharge, n (%)	34 (81 % of alive patients)

Abbreviations: BDZ, benzodiazepine; BRV, brivaracetam; LEV, levetiracetam; SE, status epilepticus.

Overall SE resolved after BRV in 32 patients (57 %). The median time to seizure cessation was 3 h. In 22 episodes seizure stopped within 6 h from BRV use (early responders; 39 %). In the remaining 10 patients SE resolved between 6 and 24 h in five cases, while in five patients SE resolved between 24 and 72 h. These last five patients have a focal NCSE.

As concern safety, treatment-emergent adverse events were observed in six patients, none was severe: in one case a transitory increase in liver enzymes was reported, while drowsiness was complained in the other cases. BRV was not withdrawn in any case. At hospital discharge of the 41 alive patients 34 (81 %) continued BRV (median dose of 100 mg).

3.1. Factors associated with brivaracetam effectiveness

Table 3 reports the comparison between SE episodes according to BRV response.

In our cohort age, gender, as well as a previous history of epilepsy were not associated to BRV response. Considering etiology, we did not observe a different response according to the etiology classification of SE episodes. As concern specific etiologies, more than half episodes of our sample were caused by a cerebrovascular disorder (18/56; 32 %), followed by CNS tumours (7/56; 13 %), head trauma (6/56; 11 %) and inducing factors in epileptic patients, such as ASMs withdrawn (6/56; 11 %). Comparing responders and non-responder patients, we did not find any etiology more prone to respond to BRV. Details are reported in **Supplementary** Table 2. The only one patient with absence status in the context of GGE showed a fast response to BRV (< 30 min) [23]. Concerning the SE semiology, we did not find differences in BRV response according to SE semiology. Also, status epilepticus prognostic scores (STESS, EMSE) didn't show a relationship with BRV response.

The median loading dose of BRV was 100 mg in responders and non-responders. Also, the weighted-adjusted loading doses in responders and non-responders showed similar mean values without significant differences.

Considering concomitant ASMs and LEV in particular no differences in BRV response emerged. Furthermore, the analysis of the order of administration showed no significant differences between responders and non-responders. However, considering the time to BRV administration from SE diagnosis a better response was found when BRV was administered earlier even though it did not reach statistical significance (24 h median time in responders *vs* 48 h in non-responders; p = 0.08).

Finally, a significant difference emerged regarding mortality, with lower death at discharge (16 %) in BRV responders compared to non-responders (42 %) (p = 0.04).

Table 3
Comparison between SE episodes according to BRV effectiveness.

Characteristic/variable	Responders (n = 32)	Non-Responders (n = 24)	p
Age, mean ± SD, y	61.1 ± 19.2	63.1 ± 19.7	1
Gender, male, n (%)	17 (53 %)	14 (58 %)	0.7
Previous Epilepsy	12 (38 %)	9 (38 %)	1
Etiology classification, n (%)			
Acute symptomatic	16 (50 %)	13 (54 %)	0.46
Remote symptomatic	7 (22 %)	3 (13 %)	
Progressive symptomatic	5 (16 %)	4 (17 %)	
Cryptogenic	0	2 (8%)	
Multifactorial	4 (13 %)	2 (8%)	
Semeiology classification, n (%)			
With prominent motor symptoms	26 (81 %)	20 (83 %)	0.8
Without prominent motor symptoms	6 (19 %)	4 (17 %)	
STESS < 3, n (%)	24 (75 %)	16 (67 %)	0.56
EMSE < 64, n (%)	14 (44 %)	8 (33 %)	0.58
Loading dose of BRV, median, mg (range)	100 (50–250)	100 (50–250)	1
Loading dose of BRV adjusted by weight, mg/kg, mean (range)	1.42 (0.5–1.9)	1.14 (0.6–1.8)	0.6
Order of treatment with BRV (after BDZ), n (%)			
First or second [early]	22 (69 %)	13 (54 %)	0.28
Third (or more)	10 (31 %)	11 (46 %)	
Time (hours) from SE diagnosis to BRV use, hours, median	24	48	0.08
LEV used prior to BRV, n (%)	7 (22 %)	8 (33 %)	0.38
Patients with refractory SE at BRV use, n (%)	20 (63 %)	16 (67 %)	0.79
Death at discharge, n (%)	5 (16 %)	10 (42 %)	**0.04**

Abbreviations: BDZ, benzodiazepine; BRV, brivaracetam; LEV, levetiracetam; SD, standard deviation; SE, status epilepticus; STESS, Status Epilepticus Severity Score; EMSE, Epidemiology based Mortality score in Status Epilepticus.

3.2. Early BRV response

Finally, we evaluated factors associated with an early SE termination defined as cessation of seizures within 6 h after BRV administration (n = 22) (Tables 4 and 5). In this analysis late-responders and non-responders were pooled together (n = 34). At univariate analysis, patients' demographics, previous epilepsy history, SE etiology, SE semiology and SE prognostics scores were not associated with an early BRV response. As far as BRV loading dose, the median loading dose of BRV was 100 mg in early-responders and in late/non-responders. In the same line, the mean weight-adjusted loading dose was 1.33 mg/kg and 1.31 mg/kg in responders and late/non-responders respectively

Table 4
Comparison between SE patients with and without an early response to BRV.

Univariate analysis	Early Responders (< 6 h, n = 22)	Late /Non-Responders (n = 34)	p
Age, mean ± SD, y	61.6 ± 18.7	63.1 ± 19.7	0.69
Gender, male, n (%)	12 (55 %)	19 (56 %)	0.92
Previous Epilepsy, n (%)	9 (41 %)	12 (35 %)	0.78
Etiology classification, n (%)			
Acute symptomatic	11 (50 %)	18 (53 %)	0.70
Remote symptomatic	5 (23 %)	5 (15 %)	
Progressive symptomatic	3 (14 %)	6 (18 %)	
Cryptogenic	0	2 (6%)	
Multifactorial	3 (14 %)	3 (9%)	
Semeiology classification, n (%)			
With prominent motor symptoms	16 (73 %)	29 (85 %)	0.31
Without prominent motor symptoms	6 (27 %)	5 (15 %)	
STESS < 3, n (%)	17 (77 %)	23 (68 %)	0.55
EMSE < 64, n (%)	11 (50 %)	11 (32 %)	0.26
Loading dose of BRV, median, mg (range)	100 (50–250)	100 (50–250)	0.66
Loading dose of BRV adjusted by weight, mg/kg, mean (range)	1.33 (0.5–2.9)	1.31 (0.6–2.9)	0.9
Order of treatment with BRV (after BDZ), n (%)			
First or second [early]	18 (82 %)	17 (50 %)	**0.02**
Third (or more), n (%)	4 (18 %)	17 (50 %)	
Early BRV administration < 6 h from SE onset, n (%)	12 (55 %)	1 (3%)	**0.0002**
LEV used prior to BRV, n (%)	3 (14 %)	12 (35 %)	0.12
Patients with refractory SE at BRV use, n (%)	13 (59 %)	23 (68 %)	0.56
Death at discharge, n (%)	4 (18 %)	11 (32 %)	0.36

Abbreviations: BDZ, benzodiazepine; BRV, brivaracetam; LEV, levetiracetam; SD, standard deviation; SE, status epilepticus; STESS, Status Epilepticus Severity Score; EMSE, Epidemiology based Mortality score in Status Epilepticus.

Table 5
Multivariate logistic regression analysis for factors associated with an early response to BRV.

Multivariate analysis	Adjusted OR	95 % CI	P
Order of treatment with BRV (after BDZ)	1.67	0.24 - 11.2	0.61
Early BRV administration < 6 h from SE onset	32.09	3.39 - 202.78	**0.002**

CI, confidence interval; OR, odds ratio.

($p = 0.9$). To note in the three patients with a fast-bolus SE resolved within 30 min.

The BRV response was faster when BRV was administered earlier, both when it was one of the first two ASMs administered (82 % vs 50 %, $p = 0.02$) and when BRV was used within 6 h from SE onset (55 % vs 3%. $p < 0.001$). Indeed, only one patient out of 34 late/non-responders received BRV within 6 h from SE diagnosis, while 12 out of 22 early-responders received BRV < 6 h from SE onset.

At multivariate analysis, only an early BRV administration (< 6 h from SE onset) was independently associated with a fast BRV response (odds ratio [OR] = 32.09, 95 % confidence interval [CI] = 3.39–202.78, $p = 0.002$).

3.3. Non-responders to IV BRV

Overall 24 SE episodes (43 %) were considered non-responders to IV BRV. Lack of response was due to different reasons: *(a)* in six cases further adjustments in concomitant ASMs occurred in the time between BRV administration and SE resolution. Thus, even if BRV was the last anti-seizure drug added in the pharmacological sequence within 72 h from SE resolution, its effectiveness could not be assumed due to changes in concomitant medications; *(b)* in one patient SE resolved after 72 -hs; *(c)* in 17 episodes (30 %) SE persisted after BRV administration, so that patients were treated with further ASMs or anesthetic drugs in 11 and six cases, respectively. Overall, in nearly half of these episodes (eight of 17) SE finally resolved, whereas the remaining patients died during SE (nine of 17). The time of administration of other ASMs/anesthetics after BRV in non-responders varied from minutes to hours. When BRV was used as a first/second- choice and SE persisted subsequent treatment lines followed shortly. In cases when BRV was used in already refractory SE episodes subsequent ASMs/anesthetics were administered at variable times. This variability reflects the judgements and choices of treating physicians to postpone anesthetic use and coma induction in selected case of SE (e.g. episodes without prominent motor phenomena or motor cases with evolution in NCSE) as well as to avoid an aggressive treatment in comorbid patients and in most severe etiologies (e.g. post-anoxic cases).

4. Discussion

In this study we have reported the mode of use, efficacy and adverse effects of IV BRV in a cohort of patients with SE collected retrospectively in different Italian centers. Up to date, this is the largest cohort amongst those reported in the literature. The demographic and clinical characteristics of the study population reflect the features of SE patients observed in Western countries [7,8]. In particular, the different aetiologies, semeiology, severity of SE are similar to those reported in previous real-world evidence studies performed in European countries and by our group [10,21]. Although the dataset Is retrospectively collected and patients have been treated in a context of clinical practice, according to the judgements and choices of individual physicians, the use of a unified clinical data collection form and the centralized revision/discussion of cases allowed to obtain homogeneous data and only 3 cases (5% of the collected cases) were excluded due to the lack of adequate electro-clinical information.

Overall 57 % of the SE episodes resolved after IV BRV administration. This percentage of effectiveness is similar to what reported in recent case-series. Namely, by Santamarina et al. [16] (23 patients; 54 %); by Kalss et al. [14] (seven patients; 57 %) and Aicua-Rapun et al. [15] (14 patients; 50 %). Notably, in the present series as well as in those previously mentioned, response rates are higher compared with that reported by Strzelczyk cohort [13] (11 patients; 27 %). It has to be noted that, in his series only refractory and super-refractory cases were treated.

Considering a more restrictive criterion of clinical efficacy, i.e. patients with response within 6 h of IV BRV administration, the responders were 22 (39 % of the total). This figure is slightly higher than the percentage of early responders identified with the same criterion by Santamarina et al. [16] (13 patients; 30 %). Analysing the resolution time of the SE episode in responders, the median was 3 h after administration, with a variability from a few minutes in the two cases where IV BRV was administered as first-line drug (instead of a BDZ) up to 48 h. SE resolution when BRV was used as first-line treatment even if anecdotical, are of particular interest since the profile of BRV suggests that it may act as fast as benzodiazepine, prolong time to next seizure and be better tolerated than benzodiazepine. The preliminary results of a recently published randomized open-label trial of IV BRV versus lorazepam for acute treatment of increased seizure activity in the epilepsy monitoring unit has shown non-inferiority of IV BRV (100 or 200 mg bolus) [24]. Even if this trial was not performed in patients with SE, and with a small number of patients, it suggests a possible role of BRV in the acute treatment of increased seizure activity as first-line drug. In our cohort the clinical motivation in the two patients in whom IV BRV was used as first-line treatment (instead of benzodiazepines) was to avoid a possible respiratory insufficiency due to the global frailty of the patient. In the 12 patients in whom IV BRV was used as second-line treatment, instead of other ASMs like phenytoin, phenobarbital, or valproate (that are currently approved in Italy to treat SE or recommended in SE guidelines), the reason was related to patients' comorbidities (hepatic or cardiovascular), or to concomitant medications.

Regarding the adverse events, BRV was generally well tolerated and we did not observe severe adverse events as reported previously. Altogether 6 patients (12 %) reported an adverse event, all were considered as mild (mostly drowsiness) and in no case the event determined BRV withdrawal. These results are completely superimposable to the ones reported in the literature [13–16].

Considering the factors associated with a response to BRV we have not observed an effect of demographic variables. In our cohort also clinical variables, such as aetiological classification and semeiology of SE have not shown association with the response to BRV: neither in the analysis of the overall responders, nor considering only early responders. Similarly, also the severity of the SE evaluated through the prognostic scores STESS and EMSE was not associated with BRV response. Regarding the semeiology and the severity of the SE episode this result is comparable to what observed in previous case-series. This implies that BRV is effective in both convulsive and nonconvulsive SE and in SE occurring in patients with different degree of clinical severity. In relation to the etiological classification, Santamarina et al. reported higher responder rates in cases with remote or progressive etiology, especially in patients with tumours, compared to cases with acute symptomatic etiology [16]. An analysis of specific aetiologies in our case mix cannot allow any conclusion due to the limited numbers of the different specific etiologies.

As far as the order of administration of BRV in the whole sample we have not found a significant difference in response rates when the BRV was administered as first or second drug compared to subsequent administrations. Moreover, analyzing specifically the concomitant use of LEV, this was not a factor associated to BRV response. Indeed, seven patients (22 %) responded to BRV despite previous administration of LEV, while this was not the case in 8 (33 % of not responders) ($p = 0.38$). There is insufficient information on whether the concomitant use of LEV

and BRV might affect the effectiveness of either drug in SE. Randomized controlled trials in focal epilepsy (N01252, N01253, and N01254) showed that BRV was less effective in patients treated with LEV [25]. However, it has been reported that BRV and LEV can act at different sites or interact with different conformational states of the SV2A protein [26]. In relation to SE and on the basis of the response observed not only in our cohort but also in those of Strzelczyk [13] (three patients who responded to BRV had already been administered LEV), Kalss [14] (in two cases), and of Santamarina [16] (in eight) it can be argued that BRV continues to be an option, despite a patient failed to respond to LEV.

Two retrospective studies [15,16] recently reported that higher weight-adjusted loading doses are associated to higher SE resolution rates (especially for loading dose > 1.8 mg/kg). We cannot confirm this finding in our population. Indeed, we did not observe a 'loading dose effect' neither in the whole sample of responders, nor considering early responders. However, we also cannot exclude this observation, since loading doses in our cohort were in the great majority of 100 mg (corresponding to a mean weight-adjusted dose of 1.3 mg/kg) with few cases of higher bolus dose. Therefore, the limited and low variability in our dataset probably precluded this kind of analysis.

Nevertheless, the results obtained in the early responders group (39 %; defined as resolution of SE < 6 h) [16] are of particular clinical relevance in an emergency context such as SE. Moreover, these findings are less subject to selection bias than the results of the whole group. In fact, in this latter group it is not possible to exclude that the resolution of the SE many hours after administration of BRV is the result of drug interactions with other ASMs, or it is due to other factors difficult to control in a retrospective study. The analysis of the variables associated with an early response has documented an association with both the administration of BRV as first/second drug and the administration of BRV within 6 h after the onset of the SE. In addition, early administration (< 6 h) was the only significant factor in the multivariate logistic regression analysis to predict an early response. This result is comparable to that obtained by Kalss et al. [14] and more recently by Santamarina et al. [16] and suggests that BRV is especially effective when used in the first hours after the onset of the SE. Notably, the effect of synaptic vesicle glycoprotein 2A modulation on the release of the GABAergic neurotransmitter could make BRV more effective in earlier stages of SE. Even if this finding needs to be confirmed with a larger number of patients and in prospective studies convergent evidences from the retrospective case-series, including our, are supporting it.

4.1. Study limitations

This is an observational study wherein treatment outcomes were reviewed retrospectively, therefore the results must be considered exploratory and cannot allow definite inferences about efficacy. Moreover, multivariable analysis in a sample of 56 patients is merely exploratory and should be considered as such. The study reflects the clinical practice and considerations of the treating physician at the time of SE observation. A possible concern is represented by the efficacy criteria that were adopted in our analysis. In literature several criteria that can drastically influence the results of observational studies have been reported [22]. However, we believe that the criteria chosen were rigorous and, importantly, their evaluation was feasible for all the patients. Another potential important limit is the confounding effect of serial ASMs administration, as each drug trial could "benefit" from the therapeutic effect of the previously used drugs. This could be especially true for ASMs with different mechanism of action. Dose-changes in concomitant medications, another source of possible bias, even if checked in medical charts can typically affect retrospective studies. However, we believe that our findings, especially the ones inherent to patients showing an early response to IV BRV are minimally influenced by all these potential biases.

5. Conclusions

In this retrospective cohort of patients, BRV proved to be useful and safe for the treatment of SE. Time to seizures resolution was shorter when it is administered in the early phases of SE, thus supporting BRV use in the early phase of SE.

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Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2021.01.014.

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