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ORIGINAL RESEARCH ARTICLE

Adjunctive Brivaracetam in Older Patients with Focal Seizures: Evidence from the BRIVAracetam add-on First Italian netwoRk Study (BRIVAFIRST)

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Abstract

Background The management of epilepsy in older adults has become part of daily practice because of an aging population. Older patients with epilepsy represent a distinct and more vulnerable clinical group as compared with younger patients, and they are generally under-represented in randomized placebo-controlled trials. Real-world studies can therefore be a useful complement to characterize the drug's profile. Brivaracetam is a rationally developed compound characterized by high-affinity binding to synaptic vesicle protein 2A and approved as adjunctive therapy for focal seizures in adults with epilepsy.

Objective The aim of this study was to assess the 12-month effectiveness and tolerability of adjunctive brivaracetam in older patients (≥65 years of age) with epilepsy treated in a real-world setting.

Methods The BRIVAFIRST (BRIVAracetam add-on First Italian netwoRk STudy) was a 12-month retrospective multicenter study including adult patients prescribed adjunctive brivaracetam. Effectiveness outcomes included the rates of seizure response (≥50% reduction in baseline seizure frequency), seizure freedom, and treatment discontinuation. Safety and tolerability outcomes included the rate of treatment discontinuation due to adverse events and the incidence of adverse events. Data were compared for patients aged ≥65 years of age ('older') vs those aged <65 years ('younger').

Results There were 1029 patients with focal epilepsy included in the study, of whom 111 (10.8%) were aged ≥65 years. The median daily dose of brivaracetam at 3 months was 100 [interquartile range, 100–175] mg in the older group and 100 [100–200] mg in the younger group ($p = 0.036$); it was 150 [100–200] mg in both groups either at 6 months ($p = 0.095$) or 12 months ($p = 0.140$). At 12 months, 49 (44.1%) older and 334 (36.4%) younger patients had a reduction in their baseline seizure frequency by at least 50% ($p = 0.110$), and the seizure freedom rates were 35/111 (31.5%) and 134/918 (14.6%) in older and younger groups, respectively ($p < 0.001$). During the 1-year study period, 20 (18.0%) patients in the older group and 245 (26.7%) patients in the younger group discontinued brivaracetam ($p = 0.048$). Treatment withdrawal because of insufficient efficacy was less common in older than younger patients [older: $n = 7$ (6.3%), younger: $n = 152$ (16.6%); $p = 0.005$]. Adverse events were reported by 24.2% of older patients and 30.8% of younger patients ($p = 0.185$); the most common adverse events were somnolence, nervousness and/or agitation, vertigo, and fatigue in both study groups.

Conclusions Adjunctive brivaracetam was efficacious, had good tolerability, and no new or unexpected safety signals emerged when used to treat older patients with uncontrolled focal seizures in clinical practice. Adjunctive brivaracetam can be a suitable therapeutic option in this special population.

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Key Points

Adjunctive brivaracetam improved seizure frequency in older patients with uncontrolled focal seizures.

During the 1-year study period, fewer patients in the older group than the younger group discontinued brivaracetam.

Adjunctive brivaracetam had good tolerability in older patients with focal seizures.

Treatment withdrawal because of insufficient efficacy was less common in older than younger patients.

No new or unexpected safety signals emerged when brivaracetam was used to treat older patients.

1 Introduction

Epilepsy affects more than 50 million people worldwide and the two highest peaks of incidence are in children and in the elderly population. The incidence of treated epilepsy, which has been estimated at 80.8 per 100,000 in the general population, rises to 85.9 and 135.4 per 100,000 in people aged 65–69 years and ≥85 years [1]. In addition to patients with new-onset epilepsy, older adults with epilepsy also include those who have been treated for many decades.

The older adults represent a growing demographic segment of the general population, and the management of epilepsy in these patients has become part of daily practice. The older adults with epilepsy represent a distinct and more vulnerable clinical group as compared with younger patients [2]. The treatment of epilepsy in the older population is challenging as physiological changes associated with aging such as the decrease of renal excretion and hepatic function, and age-related changes in receptor density and sensitivity may affect the pharmacokinetic and pharmacodynamic properties of drugs [3, 4]. The high rates of comorbidity and polypharmacy can increase the risk of drug–drug interactions, affect tolerability, and reduce medication adherence [5]. As a result of metabolic derangements, an increased incidence of cardiovascular disease, and a high potential of influencing the metabolism of drugs commonly prescribed in the elderly, first-generation and enzyme-inducing antiseizure medications (ASMs) are preferably avoided [6, 7]. Accordingly, the evaluation of the efficacy and tolerability profile of the newer ASMs in older adults has an important clinical relevance [8].

Brivaracetam (BRV) is a rationally developed compound characterized by high-affinity binding to synaptic vesicle protein 2A and approved as adjunctive therapy for focal seizures in adults with epilepsy. The BRIVAFIRST (BRIVAracetam add-on First Italian netwoRk STudy) investigated the effectiveness and tolerability of adjunctive BRV over a 1-year period in a large population of patients with focal epilepsy treated in the context of real-world clinical practice [9]. As the study included a not negligible proportion of older adult patients (aged ≥65 years), an analysis was performed to provide further evidence about the use of BRV in this age group.

2 Methods

2.1 Participants

The BRIVAFIRST was a retrospective study conducted across 62 Italian centers [9]. Adult patients attending participating centers who were prescribed BRV (March 2018–March 2020) and were receiving stable treatment with one or more ASMs during the prior 90 days were retrospectively identified. Only patients with focal epilepsy and with a 12-month follow-up after initiating BRV were included in the current analysis.

Data on demographics, clinical history, type of seizures and epilepsy [10], etiology, previous/concomitant ASMs, and baseline seizure frequency (monthly seizure frequency during the 3 months before starting BRV) were collected. Data on seizure occurrence, adverse events (AEs), and drug withdrawal were retrieved from patient seizure diaries and clinical records; visits at 3, 6, and 12 months were performed as standard practice when a new ASM is initiated. Exclusion criteria were history of alcoholism, drug abuse, conversion disorders, or other non-epileptic ictal events.

Effectiveness outcomes included the rates of seizure response (≥50% reduction in baseline monthly seizure frequency), seizure freedom, seizure worsening (>25% increase in monthly seizure frequency relative to baseline), and treatment discontinuation at 12 months. Further analyses were performed using data obtained from the visits at 3 and 6 months. Seizure freedom at each timepoint was defined as the occurrence of no seizures since at least the previous visit: at 12 months, it was considered as no seizures during the preceding 6 months, and at 3 and 6 months was defined as a lack of seizures since baseline or the 3-month visit, respectively. Safety and tolerability outcomes included the rate of treatment discontinuation due to AEs and the incidence of AEs considered BRV related by participating physicians.

2.2 Statistical Analysis

Values were presented as median [interquartile range] for continuous variables and number (percent) of subjects

for categorical variables. In this sub-analysis, demographic and baseline characteristics and study outcomes were compared between patients aged ≥65 years ('older patients') and <65 years ('younger patients'). Comparisons were made using the Mann–Whitney test or Chi-squared test, as appropriate. Results were considered significant for p values <0.05 (two sided). Data analysis was performed using STATA/IC 13.1 (StataCorp LP, College Station, TX, USA). The study is reported according to STROBE guidelines [11].

3 Results

Out of 1325 patients initially identified, 71 patients were excluded as diagnosed with generalized, combined, or unknown epilepsy and 225 because the follow-up after initiating BRV was less than 1 year at time of the current analysis. Accordingly, 1029 patients with focal epilepsy fulfilled the inclusion/exclusion criteria and were included, of whom 111 (10.8%) were aged ≥65 years. Patients aged ≥65 years were older at the time of epilepsy diagnosis, had a lower number of prior and concomitant ASMs, and a lower seizure frequency at baseline in comparison to patients aged <65 years. Baseline characteristics of participants according to class age are summarized in Table 1.

The comparison of baseline characteristics of older patients based on the epilepsy duration is provided in Table 2; short (<23 years) and long (≥23 years) epilepsy duration was defined according to the median disease duration in the group of older patients. Older patients with a long disease duration were younger at the time of epilepsy diagnosis, had a higher number of prior and concomitant ASMs, and a higher baseline seizure frequency than older patients with a short duration of epilepsy.

Table 1 Baseline characteristics of patients

Characteristics	Age class, years		p value
	<65 (n = 918)	≥65 (n = 111)	
Age, years	42 (31–52)	69 (67–74)	<0.001
Male sex	436 (47.5)	51 (46.0)	0.758
Age at epilepsy onset, years			<0.001
N[a]	917	111	
Median	12 (5–21)	47 (19–62)	
Duration of epilepsy, years			0.550
N[a]	917	111	
Median	25 (14–37)	23 (8–51)	
Type of seizure			0.352
N[a]	816	100	
Focal onset	599 (73.4)	80 (80.0)	
Focal to bilateral tonic-clonic	156 (19.1)	15 (15.0)	
Focal onset and focal to bilateral tonic-clonic	61 (7.5)	5 (5.0)	
Etiology			0.232
Structural	490 (53.4)	63 (56.8)	
Genetic	40 (4.4)	–	
Immune	10 (1.1)	1 (0.9)	
Infectious	26 (2.8)	2 (1.8)	
Unknown	352 (38.3)	45 (40.5)	
Number of previous ASMs			<0.001
N[a]	913	110	
Median	6 (3–8)	4 (2–6)	
Number of concomitant ASMs	2 (1–3)	2 (1–2)	<0.001
Baseline monthly seizure frequency[b]	6 (3–20)	2 (1–6)	<0.001

Data are median (IQR) for continuous variables, and n (%) for categorical variables

ASM anti-seizure medication, *IQR* interquartile range

[a] N refers to the total number of patients for whom data in question were available

[b] Based on the number of seizures during the 90 days before starting adjunctive brivaracetam

Table 2 Baseline characteristics of older patients according to duration of epilepsy

Characteristics	Short epilepsy duration ($n = 55$)	Long epilepsy duration ($n = 56$)	p value
Age, years	70 (66–77)	69 (67–73)	0.523
Male sex	26 (47.3)	25 (44.7)	0.781
Age at epilepsy onset, years			<0.001
Median	62 (55–70)	19 (11–31)	
Type of seizure			0.871
N[a]	51	49	
Focal onset	41 (80.4)	39 (80.0)	
Focal to bilateral tonic-clonic	8 (15.7)	7 (14.3)	
Focal onset and focal to bilateral tonic-clonic	2 (3.9)	3 (6.1)	
Etiology			0.479
Structural	34 (61.8)	29 (51.8)	
Genetic	–	–	
Immune	1 (1.8)	–	
Infectious	1 (1.8)	2 (1.8)	
Unknown	19 (34.6)	26 (46.4)	
Number of previous ASMs			<0.001
N[a]	55	55	
Median	3 (2–4)	6 (4–8)	
Number of concomitant ASMs	1 (1–2)	2 (1–3)	<0.001
Baseline monthly seizure frequency[b]	2 (1–5)	3 (1–6)	0.031

Data are median (IQR) for continuous variables, and n (%) for categorical variables. Short (<23 years) and long (≥23 years) epilepsy duration was defined according to the median disease duration in the group of older patients

ASM anti-seizure medication, *IQR* interquartile range

[a]*N* refers to the total number of patients for whom data in question were available

[b]Based on the number of seizures during the 90 days before starting adjunctive brivaracetam

The median daily dose of BRV at 3 months was 100 [100–175] mg in the older group and 100 [100–200] mg in the younger group ($p = 0.036$); it was 150 [100–200] mg in both groups either at 6 months ($p = 0.095$) or 12 months ($p = 0.140$). At 12 months, 49 (44.1%) older patients and 334 (36.4%) younger patients had a reduction in their baseline seizure frequency by at least 50% ($p = 0.110$), and the seizure freedom rates were 35/111 (31.5%) and 134/918 (14.6%) in the older and younger groups, respectively ($p < 0.001$). The rates of seizure response and seizure freedom during the follow-up in older and younger patients are shown in Fig. 1a, b, respectively. There were no differences in the rates of seizure worsening between older and younger patients at the 3-month (older: 4.3%, younger 5.4%; $p = 0.573$), 6-month (older: 4.5%, younger 2.9%; $p = 0.370$), and 12-month (older: 4.5%, younger 2.0%; $p = 0.087$) follow-up visits.

During the 1-year study period, 20 (18.0%) patients in the older group and 245 (26.7%) patients in the younger group discontinued BRV ($p = 0.048$). The reasons for treatment withdrawal were insufficient efficacy [older: $n = 7$ (6.3%), younger: $n = 152$ (16.6%); $p = 0.005$], AEs [older: $n = 12$ (10.8%), younger: $n = 87$ (9.5%); $p = 0.653$], and a combination of both [older: $n = 0$, younger: $n = 5$ (0.5%); $p = 0.436$]; in one case, BRV was discontinued because of a patient's request and one patient died because of a cause unrelated to the treatment.

Adverse events were reported by 24.2% of older patients and 30.8% of younger patients ($p = 0.185$), and were rated as mild (75.4%; older 82.6%, younger 74.7%), moderate (24.2%; older 17.4%, younger 24.9%), and severe (0.4%; older 0.0%, younger 0.4%) in intensity. The most common AEs observed in both study groups included somnolence, nervousness and/or agitation, vertigo, and fatigue (Table 3).

4 Discussion

This analysis of data from the BRIVAFIRST suggested that BRV is effective when used in clinical practice as adjunctive treatment of focal seizures in patients aged ≥65 years. Further, the known safety and tolerability profile of BRV was confirmed without any new findings of concern.

The higher seizure freedom rate and the lower incidence of treatment discontinuation due to poor efficacy observed in patients aged ≥65 years vs <65 years were consistent with prior evidence describing the greater effectiveness of BRV

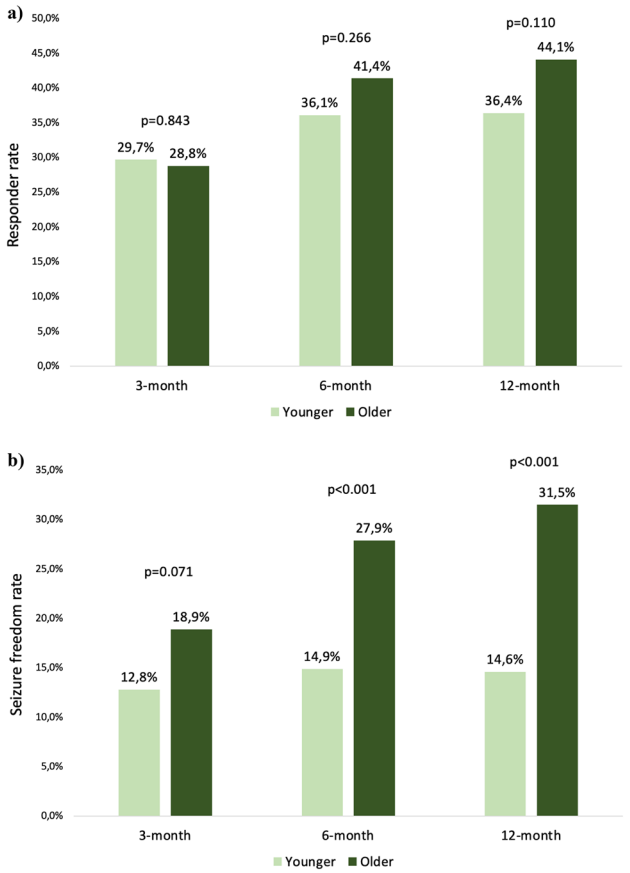

Fig. 1 Clinical response to adjunctive brivaracetam according to age class. Rates of seizure response (**a**) and seizure freedom (**b**) at 3, 6, and 12 months are reported. Seizure response was defined as a reduction in seizure frequency of ≥50% in comparison to baseline seizure frequency

Table 3 Adverse events with brivaracetam treatment according to age class

	Age class, years	
	<65	≥65
Patients with adverse events		
N[a]	782	95
n (%)	241 (30.8)	23 (24.2)
Most frequently reported adverse events[b]		
N[a]	758	94
Somnolence, *n* (%)	52 (6.9)	4 (4.3)
Nervousness and/or agitation, *n* (%)	47 (6.2)	3 (3.2)
Vertigo, *n* (%)	27 (3.6)	4 (4.3)
Fatigue, *n* (%)	23 (3.0)	3 (3.2)
Headache, *n* (%)	20 (2.6)	2 (2.1)
Aggressiveness, *n* (%)	19 (2.5)	1 (1.1)
Mood change, *n* (%)	18 (2.4)	2 (2.1)
Dizziness, *n* (%)	17 (2.2)	2 (2.1)
Sleep disturbances, *n* (%)	15 (2.0)	–
Memory disturbance, *n* (%)	12 (1.6)	2 (2.1)
Anxiety, *n* (%)	3 (0.4)	2 (2.1)

[a]*N* refers to the total number of patients for whom data in question were available

[b]Reported by ≥2% of patients in each group

Adverse events reported by <2% of patients: nausea/vomiting, tremor (all $n = 8$), stomach pain ($n = 7$), disturbances in attention/concentration ($n = 6$), diplopia/blurred vision (all $n = 5$), weight increase ($n = 4$), skin disorders, hair loss (all $n = 3$), fever, pharyngodynia, hyporexia (all $n = 2$), urinary disturbances, weight decrease, psychosis, tics, confusion, tinnitus, constipation, and abdominal pain (all $n = 1$)

in older vs younger patients [12, 13]. Importantly, patients aged ≥65 years were older at the time of epilepsy onset, had a lower number of prior and concomitant ASMs, and presented a lower baseline seizure frequency than patients aged <65 years, and these differences were particularly evident for older patients with a short epilepsy duration. These findings may suggest that older patients included in BRIVA-FIRST comprised also patients who developed epilepsy in later life and were treated relatively early in their disease course, and not only an aging population that had developed epilepsy in earlier life. The differences in baseline characteristics of patients may contribute to explain the different efficacy found across the age groups. Of note, when studies reported outcomes by age class, ASMs generally resulted in more effective outcomes in elderly patients than younger patients [14, 15].

The rates of AEs and treatment discontinuation because of AEs were not significantly different between older and younger groups, suggesting that BRV tolerability was not influenced by the age of patients. The median daily dose of BRV was lower in the older group at 3 months from starting treatment, whereas dosages were comparable in patients aged ≥65 and <65 years at the 6-month and 12-month follow-up visits. Conversely, in the BRIVA-LIFE study, the incidences of AEs and discontinuation due to AEs were numerically higher among BRV-treated patients who were 65 years of age or older in comparison to younger participants, and the final BRV dosage was significantly lower among older patients than younger patients [13]. These findings may overall indicate that a slower titration rate should be preferred in older population to minimize the risk of AEs and improve the tolerability of BRV when added to the existing therapeutic regimen.

Although the study did not consider measures specifically aimed to evaluate the impact of treatment on neuropsychological functioning, the spectrum of reported AEs suggested that BRV might have a favorable tolerability profile regarding psychiatric and cognitive effects, which are burning topics in the management of epilepsy in the older population. Indeed, behavioral and psychiatric AEs, including nervousness, aggressiveness, mood changes and anxiety,

and memory disturbances were uncommon and mostly mild among patients aged ≥65 years; further, there was no signal of sleep complaints among older participants.

BRIVAFIRST is the largest experience of BRV in clinical practice described so far, and the number of patients ≥65 years of age included in this subgroup analysis is higher than the number of older participants enrolled both in randomized placebo-controlled trials, in which the older population is typically under-represented, and other real-world cohorts. [13, 16–18]. Additional strengths were the recruitment at multiple sites and the real-world setting, which reflects the treatment approach employed under the usual circumstances of healthcare practice rather than trial protocol-defined schedules and can increase the external validity and generalizability of the findings. Limitations of this analysis should be also acknowledged, such as the open-label and retrospective design, which may have introduced potential sources of bias, and the unavailability of information about individual etiologies, seizure frequency according to seizure subtypes, comorbidities, and concomitant medications. Further, the collection of AEs as recorded during clinical visits rather than by standardized questionnaires might have resulted in under-reporting. Importantly, the absence of a control group of matching patients being treated with an alternative ASM prevents any comparisons of the efficacy and tolerability of BRV with other drugs.

5 Conclusions

Adjunctive BRV was associated with an improvement in seizure control and good tolerability in older patients with uncontrolled focal seizures and can be a suitable therapeutic option in this special population. The pharmacological profile of BRV, which does not interact with most drug-metabolizing enzymes and drug transporters and, hence, is associated with few clinically relevant drug–drug interactions [19], makes it further a potentially favorable choice for older patients. Additional studies including larger cohorts of patients and evaluating patient-reported outcomes and neuropsychological endpoints are warranted to fully explore the potential of BRV in the older population and provide more guidance for clinical decisions.

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Declarations

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Conflicts of interest/competing interests SL has received speaker's or consultancy fees from Angelini, Eisai, GW Pharmaceuticals, and UCB Pharma, and has served on advisory boards for Angelini, Arvelle Therapeutics, Bial, and GW Pharmaceuticals. LC has received consultancy fees from Eisai. MPC has received speaker's or consultancy fees from Bial, Eisai, Italfarmaco, Sanofi, and UCB Pharma. SC has participated in pharmaceutical industry-sponsored symposia for Eisai, UCB Pharma, and Lusofarmaco. VC has received speaker's or consultancy fees from Eisai and UCB Pharma. ALN has received speaker's or consultancy fees from Eisai, Mylan, Bial, Sanofi, and UCB Pharma. PP has received consulting fees or speaker honoraria from UCB Pharma and Eisai. PPQ has participated in pharmaceutical industry-sponsored clinical trials and symposia for UCB Pharma. FR has received speaker's fees from Eisai, UCB, and Livanova. ER has received fees for participation in advisory board or scientific consultation from Eisai, GW Pharmaceuticals, Bial, and UCB Pharma. LT has received speaker's or consultancy fees from Arvelle Therapeutics, Eisai, and UCB Pharma. CDB has received consulting fees or speaker honoraria from UCB Pharma, Eisai, GW Pharmaceuticals, Bial, and Lusopharma. ECI, FD, GDM, GD, GF, MF, EF, MG, FSG, OM, EM, AM, and FP have no conflicts of interest to declare.

Ethics approval This study was approved by the ethical committees at all participating sites and was conducted in accordance with the Declaration of Helsinki.

Consent to participate Informed consent was obtained from every patient and/or their parent or legal representative.

Consent for publication Not applicable.

Availability of data and material Anonymized data will be shared at the request of any qualified investigator.

Code availability Not applicable.

Author contributions SL designed and conceptualized the study, coordinated and supervised the data collection, carried out the data analyses, and drafted the manuscript. VC, EF, ALN, and EM designed and conceptualized the study, and coordinated and supervised the data collection. LC, MPC, SC, ECI, FD, GDM, GD, GF, MF, MG, FSG, OM, AM, FP, PP, PPQ, FR, ER, and LT were involved in the acquisition of data. CDB designed and conceptualized the study, coordinated and supervised the data collection, and drafted the manuscript. All authors critically revised the manuscript for important intellectual content. All authors approved the final manuscript for submission and agree to be accountable for all aspects of the work.

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