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.
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, demo-
graphic and baseline characteristics and study outcomes
were compared between patients aged ≥65 years ('older
patients') and <65 years ('younger patients'). Compari-
sions were made using the Mann–Whitney test or Chi-
squared test, as appropriate. Results were considered sig-
nificant 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 dura-
tion 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        | 917             | 111      | <0.001 |
| Median                             | 12 (5–21)       | 47 (19–62) | 0.550 |
| Duration of epilepsy, years         | 917             | 111      | 0.352 |
| Median                             | 25 (14–37)      | 23 (8–51)  |        |
| Type of seizure                     | 816             | 100      | 0.232 |
| 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                            | 490 (53.4)      | 63 (56.8) |        |
| Structural                          | 40 (4.4)        | –        |        |
| Genetic                             | 10 (1.1)        | 1 (0.9)   |        |
| Infectious                          | 26 (2.8)        | 2 (1.8)   |        |
| Unknown                             | 352 (38.3)      | 45 (40.5) |        |
| Number of previous ASMs             | 913             | 110      | <0.001 |
| Median                             | 6 (3–8)         | 4 (2–6)   |        |
| Number of concomitant ASMs          | 2 (1–3)         | 2 (1–2)   | <0.001 |
| Baseline monthly seizure frequencyb | 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

aN refers to the total number of patients for whom data in question were available

bBased 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
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,

### Table 3  Adverse events with brivaracetam treatment according to age class

| Age class, years | ≤65 | >65 |
|-----------------|-----|-----|
| Patients with adverse events | 782 | 95  |
| n (%)            | 241 (30.8) | 23 (24.2) |
| Most frequently reported adverse events | 758 | 94  |
| 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) |

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

*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)
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 a 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 Lusofarmac. 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 Liviana. 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 Lupusofarma. 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.
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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, 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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References

1. Wallace H, Shorvon S, Tallis R. Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2,052,922 and age-specific fertility rates of women with epilepsy. Lancet. 1998;352:1970–3.
2. Rohracher A, Kalss G, Kuchukhidze G, Neuray C, Leitinger M, Höfler J, et al. New anti-seizure medication for elderly epilepsy patients: a critical narrative review. Expert Opin Pharmacother. 2021;22:621–34.
3. Klotz U. Pharmacokinetics and drug metabolism in the elderly. Drug Metab Rev. 2009;41:67–76.
4. Bourdet SV, Gidal BE, Aldredge BK. Pharmacologic management of epilepsy in the elderly. J Am Pharm Assoc (Wash). 2001;41:421–36.
5. Maher RL, Hanlon JT, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf. 2014;13:57–65.
6. Brigo F, Lochner P, Nardone R, Manganotti P, Lattanzi S. Increased risk of stroke and myocardial infarction in patients with epilepsy: a systematic review of population-based cohort studies. Epilepsy Behav. 2020;104(Pt B):106307.
7. Josephson CB, Wiebe S, Delgado-Garcia G, Gonzalez-Izquierdo A, Denaxas S, Sajobi TT, et al. Association of enzyme-inducing antiseizure drug use with long-term cardiovascular disease. JAMA Neurol. 2021;78:1367–74.
8. Lattanzi S, Cagnetti C, Foschi N, Ciuffini R, Osanni E, Chiesa V, et al. Adjunctive perampanel in older patients with epilepsy: a multicenter study of clinical practice. Drugs Aging. 2021;38:603–10.
9. Lattanzi S, Canafoglia L, Canevini MP, Ciacchi S, Chiesa V, Dainese F, et al. Adjunctive brivaracetam in focal epilepsy: real-world evidence from the BRIVAracetam add-on First Italian netwoRK STudy (BRIVAFIRST). CNS Drugs. 2021;35:1289–301.
10. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:522–30.
11. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147:573–7.
12. Brodie MJ, Whitesides J, Schiemann J, D’Souza J, Johnson ME. Tolerability, safety, and efficacy of adjunctive brivaracetam for focal seizures in older patients: a pooled analysis from three phase III studies. Epilepsy Res. 2016;127:114–8.
13. Villanueva V, López-González FJ, Mauri JA, Rodríguez-Uranga J, Olivé-Gadea M, Montoya J, et al. BRIVA-LIFE Study Group. BRIVA-LIFE: a multicenter retrospective study of the long-term use of brivaracetam in clinical practice. Acta Neurol Scand. 2019;139:360–8.
14. Lawthom C, Bermejo P, Campos D, McMurray R, Villanueva V. Effectiveness and safety/tolerability of eslicarbazepine acetate in epilepsy patients aged ≥ 60 versus < 60 years: a subanalysis from the Euro-Esi Study. Neurol Ther. 2019;8:491–504.
15. Villanueva V, Garcés M, López-González FJ, Rodríguez-Osorio X, Toledo M, Salas-Puig J, et al. Safety, efficacy and outcome-related factors of perampanel over 12 months in a real-world setting: the FYDATA study. Epilepsy Res. 2016;126:201–10.
16. Lattanzi S, Cagnetti C, Foschi N, Provinciali L, Silvestrini M. Brivaracetam add-on for refractory focal epilepsy: a systematic review and meta-analysis. Neurology. 2016;86:1344–52.
17. Strzalka A, Zaveta C, von Podewils F, Möddel G, Langenbruch L, Kovac S, et al. Long-term efficacy, tolerability, and retention of brivaracetam in epilepsy treatment: a longitudinal multicenter study with up to 5 years of follow-up. Epilepsia. 2021;62:2994–3004.
18. Lattanzi S, De Maria G, Rosati E, Didato G, Chiesa V, Ranzato F, et al. Brivaracetam as add-on treatment in focal epilepsy: a world time-based analysis. Epilepsia. 2021;62:e1–6.
19. Moseley BD, Chanteux H, Nicolas JM, Laloyaux C, Gidal B, Stockis A. A review of the drug-drug interactions of the antiepileptic drug brivaracetam. Epilepsy Res. 2020;163:106327.

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