Evaluation of Efficacy, Safety, and Tolerability of Brivaracetam as Adjunctive Therapy in the Treatment of Focal Seizures: An Analysis of Mexican Patients

Original Article

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Abstract—Introduction: To evaluate, in a post-hoc subgroup analysis, the efficacy, safety, and tolerability of brivaracetam (BRV) as an adjunctive treatment compared with placebo in patients with uncontrolled focal (partial-onset) seizures recruited in Mexico. **Patients and Methods:** Seizure outcomes data were pooled from two phase III trials, NCT01339559 (N01379) and NCT00150800 (N01199). The pooled safety and efficacy data from these trials for the Mexican population were evaluated as a descriptive analysis of these core trials. **Results:** Of 179 Mexican patients who were evaluated, 67.5% completed the two trials, including a long-term follow-up that lasted more than 4 years. Of the patients who completed, 27 (96.3%) had been treated with a BRV dose of 20 mg/day, 26 (88.5%) with 50 mg/day, 21 (81.0%) with 100 mg/day, and 21 (85.7%) with 200 mg/day. After 2 years' treatment, 81% of patients had responded to treatment at a dose > 50 mg/day. In the safety analysis, only five patients discontinued because of treatment, and 26 patients had developed serious adverse events overall in the two trials. **Conclusion:** Adjunctive treatment with BRV in adults with focal seizures was effective and generally well tolerated when administered long term. **Rev Med Clin 2025;9(2):e02052509010**

Keywords—Brivaracetam, Adjunctive therapy, Focal seizure, Epilepsy, Mexico

Resumen—Evaluación de la Eficacia, Seguridad, y Tolerabilidad de Brivacetam como Terapia Adjunta en el Tratamiento de Crisis Focales: Un Análisis de Pacientes Mexicanos
Introducción: Evaluar, mediante un análisis de subgrupos post-hoc, la eficacia, seguridad y tolerabilidad de brivaracetam (BRV) como tratamiento adyuvante en comparación con placebo en pacientes con convulsiones focales (de inicio parcial) no controladas, reclutados en México. **Pacientes y Métodos:** Se agruparon los datos de los resultados de las crisis, de dos ensayos de fase III: NCT01339559 (N01379) y NCT00150800 (N01199). Los datos agrupados de seguridad y eficacia de estos ensayos en la población mexicana se evaluaron mediante un análisis descriptivo de estos ensayos pivotales. **Resultados:** De los 179 pacientes mexicanos evaluados, el 67.5% completó los dos ensayos, incluyendo un seguimiento a largo plazo de más de 4 años. De los pacientes que completaron el tratamiento, 27 (96.3%) recibieron una dosis de BRV de 20 mg/día, 26 (88.5%) con 50 mg/día, 21 (81.0%) con 100 mg/día y 21 (85.7%) con 200 mg/día. Tras 2 años de tratamiento, el 81% de los pacientes respondió al tratamiento con una dosis > 50 mg/día. En el análisis de seguridad, solo cinco pacientes interrumpieron debido al tratamiento, y 26 pacientes presentaron eventos adversos graves en general en los dos ensayos. **Conclusión:** El tratamiento adyuvante con BRV en adultos con crisis focales fue eficaz y, en general, bien tolerado cuando se administró a largo plazo. **Rev Med Clin 2025;9(2):e02052509010**

Palabras clave—Brivaracetam, Terapia adyuvante, Crisis focal, Epilepsia, México

Introduction

Antiepileptic therapy sometimes requires the use of combination treatment with multiple antiepileptic drugs (AEDs) because 20–30% of patients treated using monotherapy continue to have seizures. In addition, approximately half of all treated patients in multiple AEDs experience mild to moderate adverse reactions.[1]

Brivaracetam (BRV) is a selective, high affinity synaptic vesicle protein 2A (SV2A) ligand that has been approved by the European Medicines Agency as an adjunctive treatment for patients aged 16 years with focal (partial-onset) seizures, and by the United States Food and Drug Administration as an adjunctive treatment and monotherapy for patients aged 4 years with focal seizures (oral formulations only; BRV injection is only indicated for patients 16 years).[2,3] BRV has demonstrated efficacy and acceptable tolerability in phase IIb and III trials with treatment periods of <16 weeks' duration.[1,4]

The molecular function of SV2A has not been completely determined, but it is known to be involved in the recycling of synaptic vesicles and neurotransmission. At therapeutically relevant concentrations, BRV does not show any effect on voltage-controlled potassium channels or voltage-gated calcium channels. It also does not bind to receptors or transporters of -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid or γ-aminobutyric acid.[5] Therefore, BRV does not appear to act by conventional mechanisms of other AEDs.[5]

BRV exhibits linear pharmacokinetics at a wide range of doses, rapid and almost complete absorption, an elimination half-life of approximately 9 hours, and plasma protein binding of <20%. BRV is a 2-pyrrolidinone derivative that shares the same binding site (SV2A) as levetiracetam (LEV) but with a 10-fold higher affinity. More than 95% of the dose of BRV is eliminated in the urine, of which 8.6% remains unchanged.[6,7] Metabolism of BRV occurs mainly through hydrolysis and secondarily through hydroxylation mediated by cytochrome 2C19.[6,7]

Here, we present pooled efficacy and safety analyses from phase III trials N01379 (NCT01339559) and N01199 (NCT00150800), of fixed doses of BRV exclusively in relation to data from Mexican patients. Although N01379 and N01199 are ongoing, the last patient's last visit has occurred for Mexican patients in both trials; hence, the data presented here are final.

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Patients and Methods

Trial design

This analysis was conducted on clinical trials that evaluated the efficacy, safety, and tolerability of adjunctive BRV therapy compared with placebo in patients recruited in Mexico who had uncontrolled focal seizures. The analysis was based on data from Mexican patients who had participated in the N01199 and N01379 clinical trials, which corresponded to the follow-up phase (open-label treatment with BRV) of the double-blind, randomized trials N01193, N01253 and N01358 that compared BRV and placebo. The trials were approved by an institutional review board and all patients had given their consent.

The N01199 and N01379 open-label phase III trials, with long-term follow-up (LTFU), were conducted to evaluate the efficacy and tolerability of BRV using individualized doses with a maximum of 200 mg/day as adjunctive therapy in patients with epilepsy. These trials also evaluated the maintenance of effectiveness over a period of time.

The data were pooled from three randomized, placebo-controlled, double-blind, fixed-dose phase III trials (N01193, N01253, and N01358):

- In trial N01199, patients older than 16 years were recruited from trials N01193 and N01253 who had epilepsy and could benefit from BRV as adjunctive treatment. The conversion to monotherapy with BRV was not allowed; however, those patients who were already receiving monotherapy with BRV were allowed to continue on the same treatment.
- In trial N01379, patients (16 years) with refractory focal seizures, secondarily generalized or not, were enrolled from trial N01358.

Outcome measures

Data obtained from the Mexican patients were reviewed and evaluated in order to understand the pharmacological behavior of BRV in the Mexican population.

The efficacy population (N = 138) included patients from the primary efficacy analyses, randomized to BRV (20–200 mg/day) or placebo, who did not receive concomitant LEV at trial entry.

The effectiveness criteria reviewed were: the demographics of patients; proportion of patients who completed the trials; proportion of patients who had a reduction in seizure frequency from baseline and during LTFU up to 93 months; proportion of patients who had a seizure reduction of 50%; and the proportion of patients who had no seizures. Additionally, the AEDs used before enrollment were recorded.

Safety endpoints included adverse events (AEs), serious adverse events (SAEs), and pregnancy.

	BRV 20 mg/day n=8	BRV 50 mg/day n=31	BRV 100 mg/day n=17	BRV 150 mg/day n=60	BRV 200 mg/day n=30	BRV ≥50 mg/day n=138
Age fo patients (years)						
Mean±SD	35.3 ± 17.6	35.1 ± 9.2	36.2 ± 12.4	32.6 ± 9.9	33.9 ± 9.0	33.8 ± 9.9
Demography						
Sex, n(%)						
Female	6 (75.0)	11 (35.5)	10 (58.8)	24 (40.0)	10 (33.3)	55 (39.9)
Male	2 (25.0)	20 (64.5)	7 (41.2)	36 (60.0)	20 (66.7)	83 (60.1)
Ethnicity, n(%)						
Non-Caucasian	0	22 (71.0)	7 (41.2)	46 (76.7)	30 (100)	105 (76.1)
Navite American						
White	8 (100)	9 (29.0)	10 (58.8)	14 (23.3)	0	33 (23.9)
Mixed	0	20 (64.5)	5 (29.4)	24 (40.0)	17 (56.7)	66 (47.8)
Weight (Kg), Mean±SD	60 ± 16.2	71.3 ± 13.9	71.2 ± 16.6	70.1 ± 14.2	72.6 ± 11.9	71.0 ± 13.9
Height (cm), Mean±SD	158.3 ± 8.5	163.7 ± 7.9	163.6 ± 8.7	166.0 ± 8.9	166.9 ± 8.6	165.4 ± 8.6
BMI (Kg/m2)	24.0 ± 6.3	26.6 ± 4.8	26.6 ± 5.8	25.4 ± 4.5	26.0 ± 3.6	25.9 ± 4.6
Number of AEDs used by patients before the trials						
Previous AEDs, n(%)						
0 AEDs	4 (50.0)	11 (35.5)	5 (29.4)	15 (25)	2 (6.7)	33 (23.9)
1–2 AEDs	1 (12.5)	12 (38.7)	8 (47.1)	30 (50)	15 (50)	65 (47.1)
3–5 AEDs	3 (37.5)	8 (25.8)	4 (25.8)	12 (20)	12 (40)	36 (26.1)
>5 AEDs	0 (0)	0 (0)	0 (0)	3 (5)	1 (3.3)	4 (3.3)

Table 1: Patients' demography and previous use of AEDs.
Note: SD, standard deviation.

RESULTS

Patient baseline demographics and characteristics

In total, 138 patients in Mexico were enrolled into and completed the double-blind, placebo-controlled trials. Doses were administered at 20 mg/day or above, as stipulated in the trial protocols.

The ages of patients who completed the trial protocols are described by dose group in Table 1.

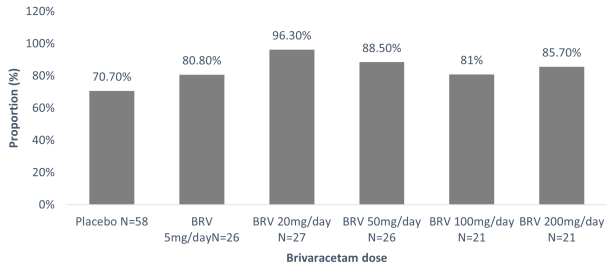

Figure 1: Percentage of patients who completed the trials according to dose maintained in treatment. N = 179, including the placebo population.
Note: BRV= Brivaracetam

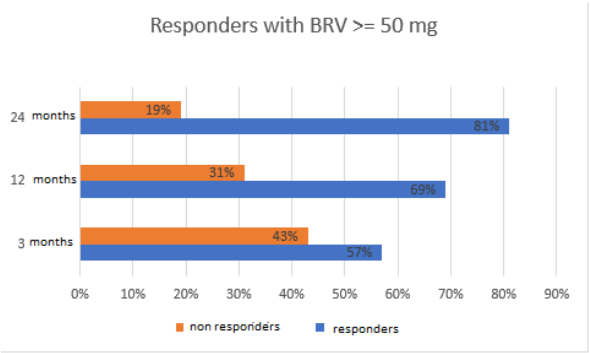

Figure 2: Responders with BRV ≥50mg.
Note: BRV= Brivaracetam

The proportions of patients who completed the placebo-controlled trials are shown in Figure 1. The number, N = 138, refers only to the population that had a BRV dose of 50 mg/day or more.

Efficacy outcomes

Table 2 show the responder rates during 3, 12, and 24 months of treatment with various doses of BRV.

Comparison of responders and nonresponders throughout the trials in patients treated with a brivaracetam dose of 50 mg/day (Figure 2).

	BRV 20 mg/day	BRV 50 mg/day	BRV 100 mg/day	BRV 150 mg/day	BRV 200 mg/day	BRV ≥50 mg/day
Proportion of responders and nonresponders during the first 3 months of treatment, by brivaracetam dose, %						
	n=8	**n=30**	**n=17**	**n=60**	**n=30**	**n=137**
Responders	4(50)	19(62)	11(65)	36(60)	13(43)	78(57)
Nonresponders	4(50)	11(38)	6(35)	24(40)	17(57)	59(43)
Proportion of responders and nonresponders after 12 months of treatment, by brivaracetam dose, %						
	n=8	**n=30**	**n=17**	**n=60**	**n=30**	**n=137**
Responders	7(80)	23(76)	13(75)	42(70)	17(56)	95(69)
Nonresponders	1(20)	7(24)	4(25)	18(30)	13(44)	42(31)
Proportion of responders and nonresponders after 24 months of treatment, by brivaracetam dose, %						
	n=4	**n=22**	**n=14**	**n=40**	**n=6**	**n=86**
Responders	4(100)	18(88)	14(100)	30(73)	4(67)	70(81)
Nonresponders	0	4(12)	0	10(28)	2(33)	30(19)

Table 2: Proportion of responders at 3, 12 and 24 months.
Note: BRV= Brivaracetam. Datos expresados en n(%).

There was a marked difference in the proportion of responders versus nonresponders.

The number of AEDs that patients used before starting the current trials is shown in Table 3.

Safety outcomes

The incidence of AEs related to treatment by dose is shown in Figure 3.

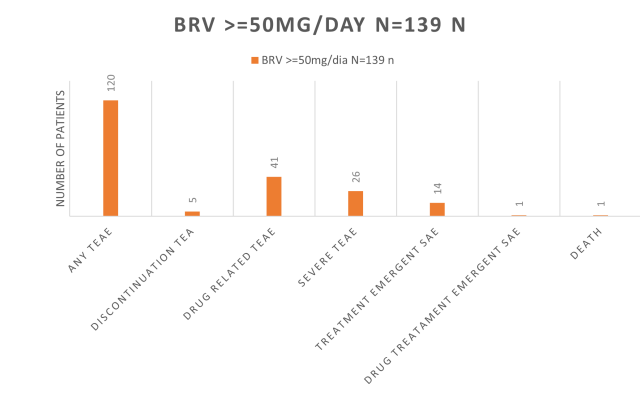

Figure 3: Number of adverse events related to brivaracetam treatment in patients treated with a dose of 50 mg/day in all of the trials. N = 139.
Note: SAE, serious adverse event; TEAE, treatment-emergent adverse event.

The most frequently observed AEs in the Mexican trial population are shown in Table 3.

During the course of the trials, there were three pregnancies reported in the Mexican trial population. All of the babies were successfully delivered and healthy.

DISCUSSION

Randomized controlled trials provide vital information on the efficacy, safety, and tolerability of an investigational treatment in a trial population. Revised results of the Mexican population participating in phase III trials demonstrated the efficacy of BRV as an adjunctive therapy in patients greater than 16 years of age.

In this analysis, as an adjunctive treatment for epilepsy, BRV demonstrated efficacy in reducing the frequency of seizures. Moreover, the results showed that adherence during the more than 4 years of treatment was greater than 80%, indicating that an AED can be used for long-term treatment.

The safety analysis showed that the AEs occurring in Mexican patients were similar to those for the overall population of both trials. Some AEs were expected, as a consequence of seasonal changes (eg, influenza), but those AEs occurring more frequently were related to effects on the nervous system, such as somnolence and anxiety, and effects on the digestive system including emesis and diarrhea.

Most enrolled patients were in their fourth decade of life, having already been treated previously with several other AEDs. Treatment with BRV as an adjunctive therapy has proved useful in the control of seizures.

CONCLUSIONS

This is the first analysis of a Mexican population for global trials, and may facilitate information gathering in respect to the environment of those living with epilepsy in Mexico. More studies are needed to fill the information gaps in this population. As with any study that pools data from more than one trial, there are limitations associated with the analysis of combined data. However, this post hoc analysis shows the efficacy of the new AED BRV.

	Patients, n(%)
Gastritis	11 (7.9)
Respiratory infection	11 (7.9)
Depression	11 (7.9)
Nasopharyngitis	14 (10.1)
Pharyngitis	16 (11.5)
Dizziness	21 (15.1)
Urinary tract infection	26 (18.7)
Headache	28 (20.1)
Influenza	41 (29.5)
Hypercholesterolemia	7 (5)
Arthralgia	7 (5)
Tonsillitis	7 (5)
Head injury	7 (5)
Myalgia	7 (5)
Insomnia	7 (5)
Dental pain	8 (5.8)
Emesis	8 (5.8)
Anxiety	8 (5.8)
Diarrhea	9 (6.5)
Somnolence	9 (6.5)
Any AE	95 (68.3)

Table 3: The most frequently observed adverse events following treatment with brivaracetam 50 mg/day. N = 139.
Note: AE, adverse event

The control of epileptic seizures in a developing country like Mexico involves several approaches to be made both by physicians and the population. However, the development of novel medicines is essential for treatment of this condition.

Author Contributions

Conceptualization, LSR, LGB, PHS, MMB, FAR; methodology LSR, MMB, FAR, GSS; formal analysis, LSR, LGB, PHS, SSS; investigation LSR, LGB, PHS, MMB, FAR; writing—original draft preparation, LGB, PHS, RFM; writing—review and editing, LSR, GSS, MMB, FAR, JGC. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

Fernando Guzman-Reyes and Jorge Villarreal-Careaga have received personal fees from UCB Pharma and several other pharmaceutical companies involved in clinical trials, but have not received any fees for the writing and development of this manuscript. Ivan Gonzalez-Gomez is a former member of UCB Mexico, and John Whitesides is employee of UCB Pharma.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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