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Brain volume loss and physical and cognitive impairment in naïve multiple sclerosis patients treated with fingolimod: prospective cohort study in Buenos Aires, Argentina

Perda de volume cerebral e comprometimento físico e cognitivo em pacientes recém-diagnosticados com esclerose múltipla tratados com fingolimode: estudo de coorte prospectivo em Buenos Aires, Argentina

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Abstract

Background The percentage of brain volume loss (PBVL) has been classically considered as a biomarker in multiple sclerosis (MS).
Objective The objective of the present study was to analyze if the PBVL during the 1st year after the onset of the disease predicts physical and cognitive impairment (CI).
Methods Prospective study that included naïve patients without cognitive impairment who initiated MS treatment with fingolimod. Patients were followed for 3 years and relapses, expanded disability status scale (EDSS) progression (defined as worsening of 1 point on the EDSS), the annual PBVL (evaluated by structural image evaluation using normalization of atrophy [SIENA]), and the presence of CI were evaluated. Cognitive impairment was defined in patients who scored at least 2 standard deviations (SDs) below controls on at least 2 domains. The PBVL after 1 year of treatment with fingolimod was used as an independent variable, while CI and EDSS progression at the 3rd year of follow-up as dependent variables.
Results A total of 71 patients were included, with a mean age of 35.4 ± 3 years old. At the 3rd year, 14% of the patients were classified as CI and 6.2% had EDSS progression. In the CI group, the PBVL during the 1st year was - 0.52 (±0.07) versus -0.42 (±0.04) in the no CI group ($p < 0.01$; odds ratio [OR] = 2.24; 95% confidence interval [CI]: 1.72–2.44).

Keywords
- Multiple Sclerosis
- Cognitive Dysfunction
- Disabled Persons
- Biomarkers
- Fingolimod Hydrochloride
- Argentina

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In the group that showed EDSS progression, the PBVL during the 1st year was - 0.59 (±0.05) versus - 0.42 (±0.03) ($p < 0.01$; OR = 2.33; 95%CI: 1.60–2.55).

Conclusions A higher PBVL during the 1st year in naïve MS patients was independently associated with a significant risk of CI and EDSS progression.

Resumo

Antecedentes A porcentagem de perda de volume cerebral (PPVC) é um biomarcador na esclerose múltipla (EM).

Objetivo Analisar se a PPVC durante o 1° ano após o início da doença prediz deterioração física (DF) e cognitiva (DC) em pacientes com EM.

Métodos Estudo de coorte prospectivo que incluiu pacientes recém-diagnosticados sem comprometimento cognitivo que iniciaram tratamento com fingolimode. Os pacientes foram acompanhados por 3 anos, sendo avaliados a presença de recidivas, progressão da Escala Expandida do Estado de Incapacidade (EDSS, na sigla em inglês) (definida como agravamento de 1 ponto na EDSS), o PPVC anual (avaliado pela avaliação de imagem estrutural de atrofia normalizada [SIENA, na sigla em inglês) e a presença de DC (avaliada no início do estudo e nos 2° e 3° anos). O PPVC no 1° ano de tratamento com fingolimode foi utilizado como variável independente.

Resultados foram incluídos 71 pacientes com idade média de 35,4 ± 3 anos. No 3° ano, 14% dos pacientes tiveram DC e 6,2% tiveram progressão de EDSS. No grupo DC, o PPVC durante o 1º ano foi - 0,52 (±0,07) *versus* - 0,42 (±0,04) no grupo sem DC ($p < 0{,}01$; razão de probabilidades [OR, na sigla em inglês] = 2,24; intervalo de confiança [IC] de 95%: 1,72–2,44). No grupo que apresentou progressão da EDSS, o PPVC durante o 1° ano foi de - 0,59 (±0,05) *versus* - 0,42 (±0,03) ($p < 0{,}01$; OR = 2,33; IC95%: 1,60–2,55).

Conclusões Um maior PPVC durante o 1° ano foi associado a um risco significativo de progressão de DC e EDSS durante o seguimento.

Palavras-chave
- Esclerose Múltipla
- Disfunção Cognitiva
- Pessoas com Deficiências
- Biomarcadores
- Cloridrato de Fingolimode
- Argentina

INTRODUCTION

Multiple sclerosis (MS) is a chronic degenerative disease that affects mostly young adults between 18 and 40 years old and is the first cause of physical disability of nontraumatic origin in several countries.[1,2] Multiple sclerosis is characterized histopathologically by the presence of inflammatory plaques associated with the presence of axonal damage.[1,3]

In MS, axonal degeneration is thought to be one important cause responsible for the irreversible progression of the disability seen in affected patients.[4–6]

Brain atrophy occurs faster in MS patients than in healthy control subjects,[7] and the atrophy is the result of gray (GM) and white matter (WM) atrophy.[7,8] The annualized rates of whole-brain and GM atrophy increased with the stage of the disease, from < 0.2% in patients with clinically isolated syndromes converting to relapsing-remitting MS (RRMS) to almost 0.4% in patients with secondary progressive MS.[8] Interestingly, GM atrophy is not uniform, being the limbic system, the temporal cortex, and deep GM the regions that showed the fastest annual rate of tissue loss in RRMS.[7,9]

The percentage of brain volume loss (PBVL) has been classically considered as a biomarker present in severe or advanced stages of the disease; however, evidence showed that brain volume loss occurs early in MS.[5,10] As a consequence, the PBVL has been identified as an early prognostic factor of the clinical and cognitive progression of MS.[11–15]

Cognitive impairment (CI) is frequently observed in MS patients even in the early stages of the disease[15] and may reflect damages to brain structures, usually detected too late to implement an effective preventive therapy.[15]

Considering the relevance of identifying early biomarkers of disease progression in terms of clinical and cognitive aspects, the objective of the present study was to analyze if the PBVL during the 1st year after the onset of MS predicts physical impairment and CI over 3 years in MS patients in a prospective cohort study in Buenos Aires, Argentina.

METHODS

Patients were prospectively included during January 2014 and January 2017. Consecutive, not random patients with a diagnosis of MS, defined according to 2010 validated diagnosis criteria, were considered for inclusion in the study.[16] Once RRMS was diagnosed and the decision to start with fingolimod was indicated, patients were invited to participate and those who accepted were included in the study. Only patients who started the treatment with fingolimod were included to homogenize the sample and avoid the possibility of the confounding factor of different treatments over brain volume measurements. In Argentina, fingolimod is available since 2010 for RRMS independently of the activity of the disease and of the duration of the disease, so it is possible to use it from the moment the patients are diagnosed.[17]

Once included, patients were followed longitudinally for at least 3 years with evaluations of clinical aspects (relapses and progression of the disease as measured by EDSS). Magnetic resonance imaging (MRI) evaluation was done 6 months (range: 4 to 7 months) after fingolimod initiation (baseline MRI), and then at the 1st, 2nd, and 3rd years after the first MRI. Cognitive evaluation was performed at study entry to exclude CI in selected patients, and then again at the 2nd and 3rd years.

Clinical parameters evaluated at baseline

Demographic and clinical characteristics of the disease were collected at the initiation of fingolimod. Age and sex data were extracted, as well as disease characteristics including age at onset, disease duration, number of relapses, EDSS scores prior exposure to fingolimod, and MRI activity defined by T2 lesion/gadolinium-enhancing lesions (pretreatment).

Follow-up evaluation

Patients were followed-up prospectively and during at least 3 years for the analysis. Evaluations collected information about a) clinical relapses, defined as the appearance of a new neurological symptom that lasts $>$ 24 hours, in the absence of clinical intercurrence, followed by a period of clinical stability or improvement of at least 30 days; b) progression of physical disability, evaluated through clinical evaluation by applying the EDSS scale. This variable was dichotomized for analysis in patients who progressed in EDSS and in those who did not progress. Progression was defined as a worsening of 1 point on the scale between one measurement and another with an interval of at least 6 months between them. To consider progression, in the case of presenting a clinical relapse, the patient must have been 3 months away from the relapse regardless of whether steroid treatment was received for the management of the acute episode; and c) new lesions in MRI. Magnetic resonance imaging included the use of 1.5 Tesla equipment, with cuts of 1.5 to 3 mm wide, obtaining sequences of T1, T2, FLAIR, and T1 with intravenous contrast. The images obtained and stored in standard storage format (DICOM) were subsequently included and processed in a semiautomated way by JIM synapse software to identify new or enlarging lesions. Magnetic resonance imaging scans were obtained from each patient at baseline (month 6 after initiation of the treatment) and at the 1st, 2nd, and 3rd years after initiation of the treatment.

To measure PBVL between the baseline MRI and the MRI obtained in the 1st year after initiation of the treatment, the structural image evaluation using normalization of atrophy (SIENA) fully automated longitudinal analysis method was used. SIENA software was used to measure cross-sectional volumes.[18,19] The PBVL was also estimated at the 2nd and 3rd years of follow-up. Regarding the neuropsychological evaluation, subjects underwent a comprehensive set of tests at study entry and then at the 2nd and 3rd years. Evaluations included the Brief Repeatable Battery of Neuropsychological tests,[20] the Stroop color-word test, and the memory comparison test (MCT). Z scores were calculated based on the mean and standard deviations (SDs) of healthy people for executive functioning (computerized self test [CST], word list generation), verbal memory (selective reminding test [SRT]), information processing speed (symbol digit modalities test [SDMT]), visuospatial memory (spatial recall test), working memory (MCT), attention (Stroop), and psychomotor speed (CST, SDMT) domains. Tests were performed by an experienced group of neurologists and a neuropshychologist (Neuropsychlogy Team, Neurology Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina) who were unaware of the MRI results, using validated translations of the neuropsychological tests.

Statistical analysis plan

Continuous data were expressed with their means and SDs. Categorical data were expressed in percentages. Demographic and clinical variables were described. At study entry, all patients had no CI after the neuropsychological assessment. The cohort was followed and reassessed at the 2nd and 3rd years. After reassessment, the cohort was subdivided into two groups representing patients with CI and patients without CI (noCI), using cognitive domain Z scores. All patients who scored at least 2 SDs below controls on at least 2 domains were designated as CI.[14] The remaining patients (scoring $>$ 2 SDs below controls) were designated as noCI. The Z scores from all cognitive domains were also averaged to form one summary statistic of average cognition. This was used to explore relations between MRI metrics and cognition but not to form patient groups. The same analysis was performed for progression of physical disability. The PBVL after 1 year of treatment with fingolimod was used as an independent variable, while CI and EDSS progression at the 3rd year follow-up were used as dependent variables. A stepwise logistic regression analysis was performed between independent and dependent variables, adjusted by age, sex, EDSS at study entry, and years of education. Forward and backward stepwise analyses were conducted using the Wald statistic as a criterion, with $p = 0.05$ for entry and $p = 0.10$ for removal. We also performed a receiver operating characteristic (ROC) curve analysis to determine the optimal sensitivity and specificity of PBVL after 1 year of treatment and CI and EDSS progression. The data analysis was performed with Stata 15 software (StataCorp, College Station, TX, USA).

The Institutional Review Board of the Hospital Italiano of Buenos Aires approved the present study (approval protocol number 2047, date of approval August 8, 2013). Informed consent was obtained from all included patients.

RESULTS

A total of 71 patients were included, 69% of whom were female ($n = 49$), with a mean age of 35.4 ± 3 years old, a mean EDSS 1.5 ± 1, a mean follow-up time of 43 ± 5 months, and mean years of education 12 ± 3. In 7 cases, fingolimod was

Table 1 Patient demographics and baseline clinical characteristics

Variables	$n = 71$
Female, *n* (%)	49 (69)
Mean age, years old ± SD	35.4 ± 3
Mean EDSS at study entry ± SD	1.5 ± 1
Mean follow-up time, months ± SD	43 ± 5
Lost during follow-up, *n* (%)	0
Years of education ± SD	12 ± 3
Switch of treatment during follow-up, *n* (%)	7 (9.8)
Switch due to treatment failure, *n* (%)	7 (9.8)

Abbreviations: EDSS: Expanded Disability Status Scale; SD, standard deviation.

switched due to treatment failure based on the decision by the principal investigators. The rest of the baseline characteristics are shown in ►**Table 1**.

Volumetric analysis was performed on the included sample.

Patients were identified according to CI and physical disability progression during the follow-up, as previously described. A total of 9 (14%) patients were classified as CI, 4 (6.2%) patients had physical disability progression, and 6 (9.3%) had relapse activity at the 3rd year.

Volumetric description according to cognitive and physical disability progression

Patients who changed the treatment due to treatment failure were excluded from the analysis.

In the CI group, a significant reduction during the 1st-year PBVL was observed compared with the noCI group after accounting for the influence of demographics and clinical variables ($p < 0.01$; odds ratio [OR] = 2.11; 95% confidence interval [CI]: 1.53–2.41) (►**Figure 1**).

Regarding physical disability, in the group that showed physical disability progression, a significant reduction during the 1st -year PBVL was also observed versus patients who did not progress ($p < 0.01$, OR = 2.13, 95%CI: 1.63–2.31) (►**Figure 2**).

In the logistic regression analysis, the PBVL during the 1st year of treatment with fingolimod was independently associated with the occurrence of CI in the initial 3 years of follow-up (OR = 2.24; 95%CI; 1.72–2.44; $p < 0.01$). This was also observed for EDSS progression (OR = 2.33; 95%CI: 1.60–2.55; $p < 0.01$) (►**Table 2** and **3**). The optimal cutoff for PBVL 1 year of treatment and CI determined by ROC analysis was - 0.49, with a diagnostic sensitivity and specificity of 84 and 91%, respectively (correctly classified 81%), and the cutoff for EDSS progression was - 0.55, with a sensitivity and specificity of 86 and 90%, respectively (correctly classified 85%).

DISCUSSION

In the present study, we found that a low number of patients progressed in terms of physical and cognitive impairment during the first 3 years of follow up. We observed that patients who progressed to CI had a significant reduction in PBVL compared with patients that did not (- 0.51 versus - 0.42) in the 1st year of treatment. Similar findings were observed when the dependent variable was progression of physical disability. A higher PBVL was observed in patients who progressed versus nonprogressive patients during the 1st year of treatment (- 0.59 versus - 0.42, respectively; $p = 0.008$). The regression analysis showed that higher PBVL during 1st first year was independently associated with CI and physical disability progression at the 3rd year. It is also worth highlighting that the included patients were naïve; however, the PBVL rate during the 1st year of follow-up exceeded - 0.5% in the entire group follow-up (►**Figures. 1** and **2**), showing how the process is present since early

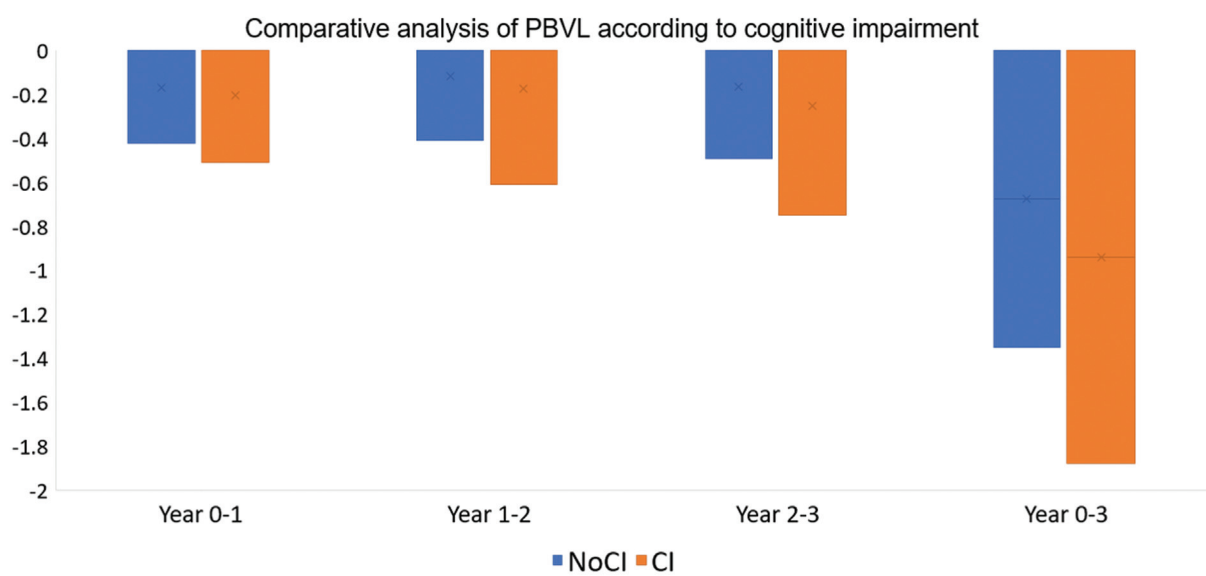

Figure 1 Comparative analysis of PBVL according to cognitive impairment. Abbreviations: CI, cognitive impairment; NoCI, no cognitive impairment; PBVL, percentage of brain volume loss.

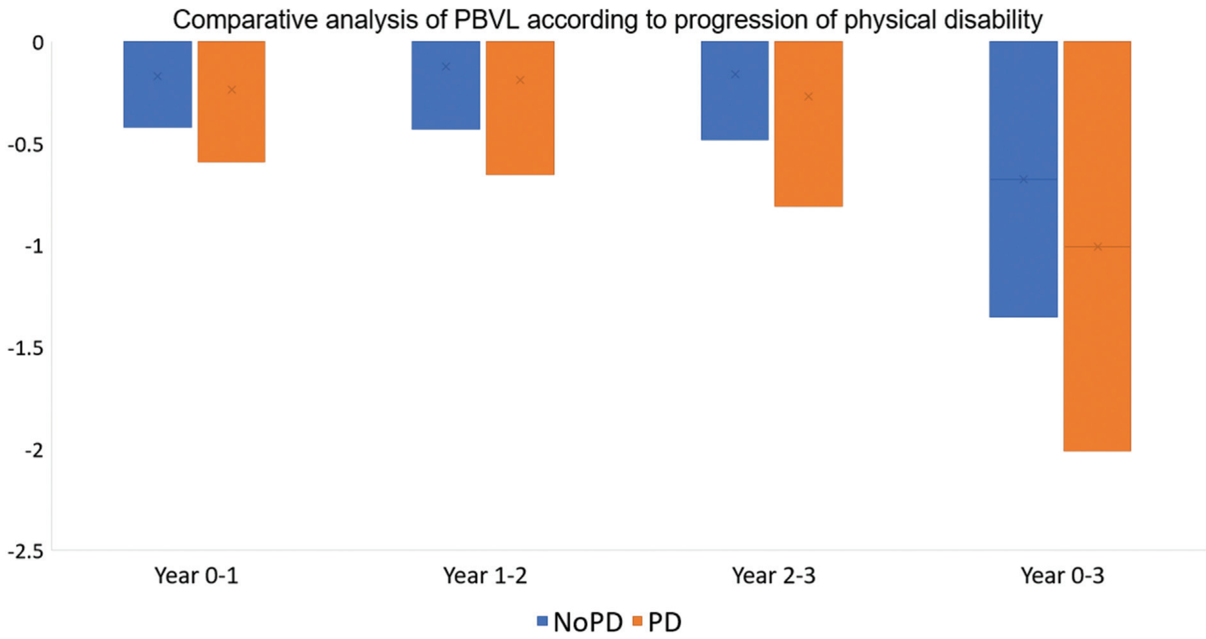

Figure 2 Comparative analysis of PBVL according to progression of physical disability. Abbreviations: NoPD, no physical disability; PD, physical disability; PBVL, percentage of brain volume loss.

Table 2 Regression analysis assessing percentage of brain volume loss after the 1st year of the treatment with fingolimod in predicting cognitive impairment at the 3rd year

Variable	OR	*p-value*	95%CI
Age	1.09	0.25	0.88–1.22
Sex	0.93	0.58	0.69–1.24
EDSS at study entry	1.17	0.22	0.91–1.43
Education	0.73	0.1	0.67–1.11
TBV	1.32	0.12	0.65–1.43
WMV	1.27	0.22	0.79–1.62
NGMV	1.57	0.09	0.98–1.9
PBVL	2.24	< 0.01	1.72–2.44

Abbreviations: CI, confidence interval; NGMV, neocortical gray matter volume; OR, odds ratio; PBVL, percentage of brain volume loss; TBV, total brain volume; WMV, white matter volume.

Table 3 Regression analysis assessing PBVL after the 1st year of treatment with fingolimod in predicting the progression of physical disability on the 3rd year

Variable	OR	*p-value*	95%CI
Age	1.12	0.24	0.92–1.19
Sex	0.97	0.56	0.78–1.15
EDSS at study entry	1.24	0.16	0.95–1.34
Education	0.76	0.09	0.56–1.26
TBV	1.45	0.10	0.79–1.57
WMV	1.23	0.19	0.82–1.51
NGMV	1.72	0.05	0.99–2.1
PBVL	2.33	<0.01	1.60–2.55

Abbreviations: EDSS, Expanded Disability Status Scale; NGMV, neocortical gray matter volume; OR, odds ratio; PBVL, percentage of brain volume loss; TBV, total brain volume; WMV, white matter volume.

moments of the disease and warrants a detailed identification process.

Several studies have investigated the association between brain volume and/or atrophy and physical disability in MS populations.[21] At a population level, brain volume has long been considered to have a better association with clinical disability than WM lesion volume. This is based on cross-sectional studies that showed negative correlations between whole brain volume/fraction and the EDSS.[22–24] Longitudinal studies, however, have demonstrated strong group-level associations between baseline brain volume and early brain atrophy, and future clinical disability.[25,26] Early brain atrophy has been found to be associated with the development of clinical disability over the medium- to long-term in multiple longitudinal studies.[8,27] Studies have demonstrated particularly strong associations between GM atrophy and physical disability.[8,27] In most of these studies, physical disability was based on the EDSS; however, in some cases, the MS Functional Composite (MSFC) was also used to assess levels of disability.[8,28] A large multicenter study in Europe that included 8 centers and 261 MS patients evaluated whether brain atrophy and lesion volumes predict subsequent 10-year clinical evolution in MS patients.[29] The study used MRI imaging at baseline and after 1 to 2 years. In the entire patient group, whole-brain and central atrophy predicted EDSS at 10 years, corrected for imaging protocol, baseline EDSS, and disease-modifying treatment. The combined model with central atrophy and lesion volume change as MRI predictors predicted 10-year EDSS with $r2 = 0.74$ in the whole group and $r2 = 0.72$ in the relapse onset group.[29] Interestingly, whole-brain atrophy was the only MRI predictor of 10-year multiple sclerosis severity score (MSSS), and the combined model explained 64.1% of the variance in MSSS.[29]

The association between cognitive impairment and MRI brain volumetric changes has been examined on multiple occasions in MS cohorts.[26,30] A large number of cross-sectional studies have been performed and associations are stronger with the GM compartment,[30–32] more specifically with deep gray matter volumes, and with cortical thickness and volume.[25,32] Longitudinal studies have revealed an association between cognitive impairment and brain atrophy, particularly GM atrophy.[21] Our study is in line with previous studies in which brain atrophy measured over the 1st year after onset of the disease was a good predictor of CI ~ 5 years later, when other relevant variables (age, sex, and as being attention and information processing speed.[33] In some MS cohorts, weak correlations between brain atrophy and cognitive performance may be explained by greater cognitive reserve in earlier disease and/or higher premorbid intelligence.[34]

Regarding fingolimod, once-daily oral fingolimod (Gilenya, Novartis, Basel, Switzerland) acts by reducing the number of recirculating autoreactive T-cells entering the central nervous system (CNS) and destroying the myelin sheath via reducing egress of these lymphocytes from the lymph nodes.[35] Fingolimod crosses the blood-brain barrier and acts directly on the S1P receptors located on these cells, leading to reduction of reactive activation of glia (which may favor naturally-occurring remyelination).[35] This mechanism of action might be responsible for the effects of fingolimod on slowing brain atrophy observed in previous studies (which, in turn, is possibly associated with CI).[35] In phase III pivotal studies, fingolimod-treated MS patients developed less brain atrophy versus patients receiving placebo both at the 1st year (– 0.50 versus – 0.65%) and at the 2nd year (- 0.84 versus -1.31%) in the FREEDOMS study,[36] and versus patients receiving interferon β-1a (IFN β-1a) over 1 year (- 0.31 versus - 0.45%) in the TRANSFORMS study.[37] The effect of fingolimod on CI in patients with MS has been assessed using the Paced Auditory Serial Addition Test (PASAT) in two pivotal phase III randomized studies, FREEDOMS and TRANSFORMS. In both these studies, a trend toward a greater proportion of correct responses on the PASAT-3 was observed in patients treated with fingolimod compared with those receiving placebo (FREEDOMS) or IFN β-1a (TRANSFORMS, where the difference versus IFN β-1a was significant, with $p = 0.049$).[36,37] Our study is in line with the recently published GOLDEN pilot study, which included RRMS patients with CI randomized (2:1) to fingolimod (0.5 mg daily) / IFN β-1b (250 µg every other day).[38] The objective of that study was to evaluate the stability on cognitive performance of patients with CI under fingolimod. Overall, 157 patients were randomized. Patients randomized to fingolimod showed improvements in all cognitive parameters evaluated after 18 months of follow-up.[38]

The main limitation of our study is that information comes from a single center. However, the prospective form of data collection and the follow-up time (at least 36 months) increase certainty regarding effectiveness and safety issues during the follow-up. Another limitation is that we only included patients under fingolimod; however, this limitation allows us to control the possibility of a confounding factor of brain volume loss due to a different mechanism of action of treatments used for MS.

In summary, we observed CI and disability progression during the first 3 years of follow-up were low in naïve patients who started treatment with fingolimod. In patients who progressed in terms of CI and physical disability, the rate of PBVL during the 1st year of treatment was significantly higher than that observed in patients who did not, being a useful biomarker of worse prognosis.

Our results represent one of the first postmarketing studies conducted in Argentina and its region on the use of fingolimod in a real-world setting.

Authors' Contributions

JIR, LP: Data collection, data management, data analysis, and manuscript review; FS: Data collection, data management, and manuscript review; AP, EC: Data collection and manuscript review.

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Conflict of Interest

Cristiano E., Rojas, J. I.,, and Patrucco L. have received fees for consultations as scientific advisory board members and for travels to meetings, conferences, and clinical trials of the following companies: Avanir, Bayer, Biogen, Merck, Novartis, and Teva. Pappolla A. and Sánchez F. have no conflict of interests to declare.

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