Predictive value of early brain atrophy on response in patients treated with interferon β

OPEN

ABSTRACT

Objective: To investigate the association between brain volume loss during the first year of interferon treatment and clinical outcome at 4 years.

Methods: Patients with multiple sclerosis initiating interferon β were clinically evaluated every 6 months for the presence of relapses and assessment of global disability using the Expanded Disability Status Scale (EDSS). MRI scans were performed at baseline and after 12 months, and the percentage of brain volume change (PBVC), brain parenchymal volume change (BPVc%), gray matter volume change (GMVc%), and white matter volume change (WMVc%) were estimated. Patients were divided based on the cutoff values for predicting confirmed EDSS worsening obtained by receiver operating characteristic analysis for all atrophy measurements. Survival curves and Cox proportional hazards regression to predict disability worsening at last observation were applied, adjusting for demographic, clinical, and radiologic variables.

Results: Larger PBVC and WMVc% decreases were observed in patients with disability worsening at 4 years of follow-up, whereas no differences were found in BPVc% or GMVc%. Cutoff points were obtained for PBVC (~0.86%; sensitivity 65.5%, specificity 71.4%) and WMVc% (~2.49%; sensitivity 85.3%, specificity 43.8%). Patients with decreases of PBVC and WMVc% below cutoff values were more prone to develop disability worsening (unadjusted hazard ratio [HR] 3.875, p = 0.005; HR 4.246, p = 0.004, respectively). PBVC (HR 4.751, p = 0.008) and the interaction of new T2 lesions with WMVc% (HR 1.086, p = 0.005) were found to be independent predictors of disability worsening in the multivariate analysis.

Conclusions: At the patient level, whole-brain and white matter volume changes in the first year of interferon β therapy are predictive of subsequent clinical evolution under treatment. Neurology Neuroimmunol Neuroinflamm 2015;2:e132; doi: 10.1212/NXI.0000000000000132

GLOSSARY

ARR = annualized relapse rate; BPV = brain parenchymal volume; BPVc% = brain parenchymal volume change; CEL = contrast-enhanced lesions; CI = confidence interval; CW = confirmed worsening; EDSS = Expanded Disability Status Scale; GMV = gray matter volume; GMVc% = gray matter volume change; HR = hazard ratio; MS = multiple sclerosis; NEL = new or enlarging lesions; PBVC = percentage of brain volume change; RRMS = relapsing-remitting MS; WMV = white matter volume; WMVc% = white matter volume change.

Therapy initiation with interferon β is still the first step in the treatment of many patients with multiple sclerosis (MS). However, patients’ response to interferon is variable, and treatment failure may lead to irreversible increases in disability before appropriate therapy switches are implemented.

Unfortunately, it is still not possible to accurately predict which patients will have a good response to therapy, so refinement of early markers of failure to respond to interferon β is necessary.

From the Servei de Neurologia/Neuroimmunologia (F.C.P.-M., J.S.-G., A.V.-J., J.R., M.T., X.M.) Multiple Sclerosis Centre of Catalonia (Cemcat) and Unitat de Ressonància Magnètica (Servei de Radiologia) (C.A., D.P., A.R.), Hospital Universitari Vall d’Hebron, Barcelona, Spain; and Departament de Medicina (F.C.P.-M.), Universitat Autònoma de Barcelona, Barcelona, Spain.

Funding information and disclosures are provided at the end of the article. Go to Neurology.org/nn for full disclosure forms. The Article Processing Charge was paid by the authors.

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At the trial level, on-therapy development of whole-brain atrophy and the presence of new lesion activity have been associated with the impact of such therapy on disability in a recent meta-analysis. However, at the patient level, less is known about the clinical implications of whole-brain or tissue-specific brain volume decreases and at what level this decline is clinically meaningful.

For that reason, we sought to analyze clinical implications of whole-brain and tissue-specific brain volume dynamics early after therapy onset in a cohort of patients initiating treatment with interferon β.

**METHODS** Patient disposition and clinical measurements.

A total of 124 patients with MS initiating interferon β were selected from an ongoing long-term longitudinal study at the MS Center of Catalonia since 2001 according to the following criteria: (1) more than 48 months since the beginning of treatment with interferon β; (2) no previous immunosuppressant or immunomodulatory drug other than interferon β; and (3) availability of brain MRI examinations performed in the 3 months prior to and 12 months after therapy onset. Eighteen of 124 patients were excluded because of incomplete MRI protocol and/or suboptimal imaging quality; 1 patient was lost to follow-up before 24 months and 2 were lost to follow-up before 48 months (figure e-1 at Neurology.org/nn).

The only second-line treatment approved at the time of observation was mitoxantrone; none of the patients received any currently available second-line therapies or immunosuppressants during the time of observation.

Clinical definitions of annualized relapse rate (ARR) and confirmed Expanded Disability Status Scale (EDSS) worsening (CW) are described in appendix e-1. All patients were clinically assessed for EDSS and the presence of relapses on a 3- to 6-month basis. Diagnosis of MS was made according to the 2001 McDonald criteria.

**MRI acquisition and analysis.** MRI scans were performed in each patient within 3 months before initiation of interferon β treatment (baseline MRI scan) and approximately 12 months after therapy began (follow-up MRI scan). Pulse sequences are described in appendix e-1 and are in line with the current recommendations of the Spanish Society of Neurology for the correct interpretation of MRI studies from patients with MS.4 Follow-up T2-weighted scans were compared with the baseline scan to assess the presence of new or enlarging lesions (NEL). In both baseline and follow-up scans, number and volume of hyperintense T2 lesions and contrast-enhancing lesions (CEL) were determined using the Disipmage software package.7 Baseline and follow-up MRI scans from each patient were analyzed to calculate brain parenchymal volume (BPV), gray matter volume (GMV), and white matter volume (WMV). Changes from baseline to follow-up MRI scans were determined for each volume. Finally, we analyzed the percentage of brain volume change (PBVC) in all patients (n = 105). (Due to segmentation errors produced when determining tissue-specific brain volumes [GMV, WMV], only 84 patients were included in the analysis of tissue-specific variables.) Software specifications are described in appendix e-1.10,11

**Statistical analysis.** The analysis was performed using SPSS v19.0 (SPSS, Chicago, IL). The Kolmogorov-Smirnov test was used to assess normality, except if n < 30, when the Shapiro-Wilk test was used instead. Nonparametric tests were preferred when a normal distribution was not assumed.

Cutoff values for all global and tissue-specific brain volume changes were obtained as described in appendix e-1. Survival curves of time to CW for each group were compared using the log-rank test. Cox proportional hazards model ("enter" method) to predict CW after 4 years of follow-up was applied to adjust the cutoff values for global and tissue-specific brain volume changes for age, sex, time from first relapse to treatment, ARR before treatment, presence of further MS attacks within the first year of follow-up, number of NEL after 12 months of therapy, presence of CEL in either baseline or follow-up MRI scan, and baseline volume values. Statistical significance was set at p < 0.05. No attempt to correct for multiple comparisons was made in order to avoid type II errors.12

**RESULTS** Sample features at baseline. Baseline demographic, clinical, and brain volume features of the patients included in the study are presented in table 1. Baseline and follow-up lesion-related MRI parameters are shown in table 2.
Clinical evolution after interferon β initiation and changes in lesion parameters according to subsequent clinical evolution are shown in appendix e-2 and tables e-1 and e-2.

First-year brain volume change in the whole sample and according to subsequent clinical evolution. Whole sample. Decreases were observed for PBVC (n = 105; mean −0.829%, SD 1.128, p < 0.001). Statistical Parametric Mapping 8–derived parameters (n = 84) showed decreases for BPV change (BPVc%) (mean −0.476%, SD 1.340, p = 0.002) and GMV change (GMVc%) (mean −0.727%, SD 2.123, p = 0.002) but not for WMV change (WMVc%) (mean −0.099%, SD 2.623, p = 0.730) (figure 1).

Summary of first-year volume changes. No differences for any global or tissue-specific measures were observed between patients with or without relapses after 2 or 4 years or with or without CW after 2 years. Larger PBVC and WMVc% decreases within the first year of treatment were observed in patients with CW at 4 years of follow-up, whereas no differences were found in BPVc% or GMVc% (figure 1, table 3).

Predictive models of disability progression on interferon β therapy. Selection of cutoff points for change in brain volume measurements. Cutoff points for brain volume changes associated with CW at 4 years in the univariate analysis (PBVC and WMVc%) were obtained by receiver operating characteristic curves and were as follows (figure e-2): PBVC cutoff = −0.86% (sensitivity 71.4%, 95% confidence interval [CI] 50%–86.2%; specificity 65.5%, 95% CI 54.8%–74.8%) and WMVc% cutoff = −2.49% (sensitivity 85.3%, 95% CI 75%–91.8%; specificity 43.8%, 95% CI 23.1%–66.8%).

Survival analysis. For PBVC, Kaplan-Meier curves (figure 2) up to 4 years showed an early separation of the event-free lines. Patients whose PBVC decreased below the −0.86% cutoff were more prone to develop CW during the 4 years of follow-up (unadjusted hazard ratio [HR] 3.875, 95% CI 1.5–10.0, p = 0.005). For WMVc%, Kaplan-Meier curves (figure 2) displayed similar results, indicating that patients losing more than 2.49% of WMV in the first year of interferon β therapy were more likely to develop confirmed EDSS increases during the 4 years of follow-up (unadjusted HR 4.246, 95% CI 1.27–9.20, p = 0.015).

Multivariate analysis. Signs of a moderate interaction between NEL and the presence or absence of a WMVc% of −2.49% or lower were detected, but not for PBVC. Although the likelihood of having CW after 4 years of follow-up increases with NEL for both groups of WMVc%, it increases faster for the group with WMVc% ≤ −2.49% (figure e-3), so these variables were expressed as an interaction in the regression model. Two models for the Cox proportional hazards regression were used (figure 3). Common variables used are those already explained in the methods section. Model 1 (n = 105) showed that an annual PBVC ≤ −0.86% after treatment (adjusted HR 4.647, 95% CI 1.479–14.603, p = 0.009), the number of NEL, and the presence of relapses during the first year of therapy were independent predictors for developing CW. Model 2 (n = 84) indicated that the interaction between NEL and annual WMVc% ≤ −2.49% after treatment (adjusted HR 1.073, 95% CI 1.012–1.137, p = 0.018), together with the presence of relapses in the first year of therapy, were independent predictors for CW. PBVc% and GMVc%, either alone or in combination, were not found to predict sustained progression as per the models above (data not shown).

**DISCUSSION** The present study aimed to investigate the association between the development of global and regional (gray and white matter) brain atrophy during the first year of treatment and evolution of disability in the medium-term. Our results showed that during the first year of therapy with interferon β, patients with relapsing-remitting MS (RRMS) who have annual global brain volume losses beyond −0.86% are at a higher risk of CW at 4 years than those above that threshold. In addition, the effect of the number of new or enlarged T2 lesions on the probability of having CW seems to be enhanced in those patients who develop WMV decreases in excess of −2.49% after the first year of therapy.
Currently, clinical (presence of attacks, confirmed disability worsening) and MRI lesion–related parameters (presence of new T2 or contrast-enhancing lesions) are used in combination to detect treatment failure. In this regard, MRI lesion activity has gained ground as a surrogate marker in disease activity monitoring and for the detection of patients with suboptimal response to therapy, as it is now fully integrated into virtually all proposed definitions of treatment failure. However, a neurodegenerative process due to neuroaxonal damage, not only at MRI-visible lesion sites but also in normal-appearing brain tissue, is already present from very early in the disease course and is thought to be responsible for the development of irreversible disability. Therefore, brain volume loss (atrophy), a measure of brain tissue integrity and a proxy for neurodegeneration, has been proposed as a potential prognostic tool in MS on the grounds that quantification of MS lesions alone does not fully reflect the clinically relevant pathogenic processes. Brain volume is relatively easy to measure through conventional MRI, for which sufficiently sensitive and reproducible methods have been developed, and seems to correlate with established neurologic disability better than lesion-related measurements.

Global brain atrophy is a reliable marker for predicting CW at the trial level. A recent meta-analysis that evaluated a large number of recently performed
clinical trials showed that the treatment effect on global brain atrophy explained almost 50% of the variance in treatment effect on 2-year disability worsening.\textsuperscript{5} Nevertheless, to our knowledge, no threshold of clinically significant volume loss at a patient level has been proposed, and its exact clinical impact on prognosis has not been reported.

Global brain atrophy rates vary from \(-0.7\%\) to \(-1.2\%\) per year in patients with RRMS treated with placebo,\textsuperscript{20} compared to \(0.18\%\) per annum in healthy controls.\textsuperscript{21} Our study proposes cutoff values of global and WMV changes for the individual prediction of further CW during the first 4 years of follow-up after starting treatment with interferon \(\beta\).\textsuperscript{22}

It is important to highlight that the positive predictive values of the reported brain atrophy cutoff points for predicting CW are low (PBVC \(34\%), WMVc\% \(41.2\%\)), which means that an isolated value of volume change below the cutoff is a poor marker of progression and that the occurrence of new attacks or new lesions also contributes significantly to predictive models of clinical progression. This may be due to the pseudoatrophy that occurs during the first year of treatment, which seems to be more apparent in high-dose interferon \(\beta\) regimens\textsuperscript{23,24} than low-dose regimens.\textsuperscript{25,26} Pseudoatrophy is brain volume reduction due to the loss of cerebral water content and the resolution of the inflammatory phenomena and not as a consequence of irreversible tissue injury.\textsuperscript{27} This effect could be mitigated by using scans performed at least 3 months after starting therapy as baseline.\textsuperscript{28} On the contrary, the negative predictive values of the reported brain atrophy cutoff values are high (PBVC \(90\%), WMVc\% \(87\%\)), indicating that these measurements could be an important early prognostic tool in the clinical setting, since patients displaying volume changes above the cutoff values have a very low probability of CW in the subsequent follow-up. Because of simpler calculation and a higher HR than WMVc\%, PBVC could be the measure of choice for use in clinical practice settings. Finally, the acquisition of a second-year MRI scan would add useful information and would further help

### Table 3 Summary of the first-year brain volume changes according to clinical evolution after 4 years

<table>
<thead>
<tr>
<th>According to the presence of further relapses</th>
<th>According the presence of confirmed EDSS worsening</th>
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<tbody>
<tr>
<td>Relapse-free patients, Mean (SD)</td>
<td>Progression-free patients, Mean (SD)</td>
</tr>
<tr>
<td>Presence of further attacks, Mean (SD)</td>
<td>Presence of further attacks, Mean (SD)</td>
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<tr>
<td><strong>PBVC</strong></td>
<td><strong>BPVC</strong></td>
</tr>
<tr>
<td>(-0.751 (0.965))</td>
<td>(-0.901 (1.287))</td>
</tr>
<tr>
<td>(&lt;0.001)</td>
<td>(&lt;0.001)</td>
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<tr>
<td><strong>GMVc%</strong></td>
<td><strong>BPVc%</strong></td>
</tr>
<tr>
<td>(-0.874 (1.974))</td>
<td>(-0.539 (1.432))</td>
</tr>
<tr>
<td>(0.010)</td>
<td>(0.026)</td>
</tr>
<tr>
<td><strong>WMVc%</strong></td>
<td><strong>GMVc%</strong></td>
</tr>
<tr>
<td>(-0.009 (0.482))</td>
<td>(-0.874 (1.974))</td>
</tr>
<tr>
<td>(0.983)</td>
<td>(0.010)</td>
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**Percentage changes are expressed as: 100 \times (follow-up MRI volume − baseline MRI volume)/baseline MRI volume.**

\(a\) One-sample \(t\) test.

\(b\) Mann-Whitney \(U\) test.
Figure 3 Cox proportional hazards regression models for predicting confirmed Expanded Disability Status Scale worsening at 4 years of follow-up

Hazard ratios are plotted with 95% confidence interval. (A) Model including percentage of brain volume change (PBVC) categorized into ≤ -0.86% or higher. (B) Model including percentage of white matter volume change (WMVc%) categorized into ≤ -2.49% or higher as an interaction with number of new or enlarged T2 lesions after 12 months of therapy (NEL). ARR = annualized relapse rate as the mean of relapses of the 2 years before starting treatment; Bas. BPV = baseline brain parenchymal volume; Bas. WMV = baseline white matter volume; CEL = contrast-enhancing lesions; TIT = time in years since the first attack until the start of therapy with interferon β; WMVc% = (100 × [first year WMV – baseline WMV]/ [baseline WMV]).

An important limitation is that the spatial resolution of the MRI scans is not isotropic because images were obtained from a protocol first implemented in 2001 and volumetric 3D pulse sequences were seldom applied in MS clinical practice. Although 3D isotropic sequences reduce partial volume errors more efficiently than nonisotropic T1 sequences, the latter have been applied to extract brain volume measures in a number of studies and by our own group.16,25,36–38 Also, segmentation techniques have a poor scan-rescan accuracy for longitudinal studies compared with registration methods such as SIENA.39 This might explain the robustness of the PBVC measure compared with tissue-specific volumes in our series. The relatively low proportion of patients with CW may also have increased dispersion of the sample and therefore affected the accuracy of tissue-specific measurements. Type I error cannot be ruled out due to the number of correlations performed; however, the verisimilitude of all the associations reported plus the multivariate analysis would argue against these findings being spurious. However, corrections for multiple comparisons were not performed statistically, and a substantial
proportion of the MRI-clinical correlations assessed were not significant. It is thus recommended that these results be confirmed in future studies. A further limitation of the present study, which is related to its observational design, is the lack of a placebo arm, so we cannot definitely conclude whether the results are due to natural history or real response to treatment.

Our study indicates that brain volume changes in the first year of interferon β therapy are predictive of subsequent clinical evolution under treatment along with other clinical and MRI-derived measurements and proposes cutoff values for reference in future confirmatory studies.

AUTHOR CONTRIBUTIONS
Dr. Francisco Carlos Pérez-Miralles contributed to selecting the patients, analyzing the clinical and volumetric MRI data, developing the statistical studies, discussing the results, and writing the manuscript. Dr. Jaume Sastre-Garriga contributed to designing the study, selecting the patients, analyzing the clinical and volumetric MRI data, developing the statistical studies, discussing the results, and writing the manuscript. Dr. Angela Vidal-Jordana contributed to acquisition of clinical data, analyzing the clinical and volumetric MRI data, and drafting/revising the manuscript for content. Dr. Jordi Río contributed to acquisition of clinical data and drafting/revising the manuscript for content. Dr. Cristina Auger contributed to analyzing the MRI data and drafting/revising the manuscript for content. Ms. Déborah Pareto contributed to analyzing the MRI data and drafting/revising the manuscript for content. Dr. Mar Tintoré contributed to acquisition of clinical data and drafting/revising the manuscript for content. Dr. Alex Rovira contributed to analyzing the MRI data, discussing the results, and drafting/revising the manuscript for content. Dr. Xavier Montalban contributed to acquisition of clinical data, discussing the results, and drafting/revising the manuscript for content.

STUDY FUNDING
No targeted funding reported.

DISCLOSURE
F.C. Pérez-Miralles received speaker honoraria from Almirall, Biogen Idec, Genzyme, Novartis, Sanofi-Aventis, and Teva. J. Sastre-Garriga is on the scientific advisory board for Novartis, Bayer-Schering, Teva, Merck-Serono, and Biogen; received speaker honoraria from Novartis, Sanofi-Aventis, Teva, Serono Simposia International Foundation, Lundbeck, Biogen, Merck-Serono, Universitat Jaume I de Castelló, Almirall, Bayer-Schering, and Genzyme; is on the editorial board for Multiple Sclerosis Journal and Latin American Multiple Sclerosis Journal; has consulted for Novartis, Sanofi-Aventis, Teva, Serono Simposia International Foundation, Lundbeck, Biogen, Merck-Serono, Universitat Jaume I de Castelló, Almirall, Bayer-Schering, and Genzyme; is on the editorial board for Multiple Sclerosis Journal and Latin American Multiple Sclerosis Journal; has consulted for Novartis, Sanofi-Aventis, Teva, Serono Simposia International Foundation, Lundbeck, Biogen, Merck-Serono, Universitat Jaume I de Castelló, Almirall, Bayer-Schering, and Genzyme; is on the editorial board for Multiple Sclerosis Journal and Latin American Multiple Sclerosis Journal; has consulted for Almirall, Bayer-Schering, Serono, Biogen, and Teva. C. Auger and D. Pareto report no disclosures. M. Tintoré is on the advisory board for Biogen, Roche, Sanofi, Trophos, and Lilly; is on the editorial board for Multiple Sclerosis Journal, Revista de Neurologia, and Therapeutic Advances in Neurological Disorders; has consulted for Novartis, Teva, Merck-Serono, Biogen, Bayer-Schering Pharma, GSK, Almirall, Neurotech Pharma, Actelion, Genzyme, Octapharma, Receptos, Roche, Sanofi-Aventis, Trophos, and Lilly; received travel funding from Novartis, Teva Pharmaceutical, Merck-Serono, Biogen, Bayer-Schering Pharma, GSK, Almirall, Neurotech Pharma, Actelion, Genzyme, Octapharma, Receptos, Roche, Sanofi, Trophos, and Lilly; and has received research support from Multiple Sclerosis Foundation of Barcelona. Go to Neurology.org/nm for full disclosure forms.

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Francisco Carlos Pérez-Miralles, Jaume Sastre-Garriga, Angela Vidal-Jordana, et al.
*Neurol Neuroimmunol Neuroinflamm* 2015;2;
DOI 10.1212/NXI.0000000000000132

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