Cortical atrophy and cognitive outcomes in relapsing MS patients treated with ofatumumab: a real-world longitudinal study

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INTRODUCTION

Among disease modifying treatments (DMTs) for multiple sclerosis (MS), ofatumumab (OFA) represents a fully human anti-CD20 monoclonal antibody offering a targeted B-cell depleting approach with convenient subcutaneous administration.

Magnetic resonance imaging (MRI) biomarkers, including measures of brain atrophy and cortical thickness obtained with semi-automated tools, are established indicators of treatment response in multiple sclerosis (MS) research, yet their use in clinical routine is still limited.

AIM

This study aimed to:

collect real-world data on non-conventional MRI metrics in patients treated with OFA.

Explore cognitive and fatigue outcomes in the same cohort and evaluate their correlations with MRI metrics.

METHODS

We included relapsing MS (RMS) patients followed at the MS centre of Foggia, Italy, who initiated treatment with OFA between January 2022 and June 2024, and with at least 12 months follow-up. Data were collected at baseline within 3 months from therapy start (T0) and 12 months after (T1).

All patients had at least two brain MRI scans available, performed at T0 and T1; additional follow-up scans were included when available. Volumetric analysis was performed on MPRAGE images, after lesion segmentation and filling with lesion prediction algorithm (LPA) from LST toolbox version 3.0.0. for SPM, with the longitudinal stream of FreeSurfer (version 8.0). Volumes were normalized to estimated total intracranial volume (eTIV) to account for between-patient differences in head size.

Brief International Cognitive Assessment for MS (BICAMS), with its components Symbol Digit Modalities Test (SDMT), California Verbal Learning Test-II (CVLT-II) and Brief Visuospatial Memory Test- Revised (BVMT-R), was performed at T0 and T1.

RESULTS

73 patients were included in the analysis, 50 (68.5%) females, with a mean age of 36.9 ± 9.9 years. The mean follow-up was 24.5 ±8.7 months.

A linear mixed-effect model was built to estimate the longitudinal rates of global and regional atrophy during follow-up. Log-transformed brain measurements at each given timepoint were used as dependent variables, and the following variables were included as covariates: time from baseline (treatment start with OFA), sex, eTIV, age and disease duration at baseline. An annual decline of approximately 2.1% in brain parenchymal fraction (BPF) (95% CI, -3.1 to -0.9, p < .001), was observed, with longer disease duration and older age also predicting lower BPF (Fig. 1).

For cortical thickness, the same model was built with regions of interest (ROIs) from the Desikan-Killiany atlas as dependent variables, and time from baseline (treatment start with OFA), sex, age and disease duration at baseline as covariates. The annual rate of cortical thinning was -1.8 (95% CI, -2.9 to -0.7, p 0.001); annual percentage changes in each ROI are represented in Fig. 2-3.

Paired-samples t-tests comparing T0 to T1 z-scores from BICAMS evaluation showed significant but modest within-subject improvements for SDMT z-score (mean difference = 0.5, t-test = 5.7, p < .001), CVLT-II z-score (mean difference = 0.5, t-test = 3.7, p < .001),and BVMT-R z-score (mean difference = 0.5, t-test = 5.8, p < .001) (Fig. 4).

Pearson's correlation showed a positive association between baseline BVMT-R z-scores and baseline cerebellar volume (r = 0.3, p = 0.007), deep grey matter volume (r = 0.3, p = 0.03) and hippocampal volume (r = 0.2, p = 0.04).

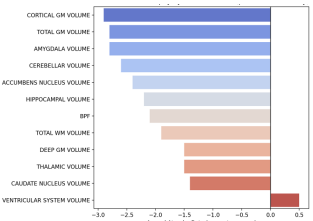

Figure 1. Annual atrophy rate for global and regional brain measurements. BPF, brain parenchymal fraction; GM, grey matter; WM, white matter.

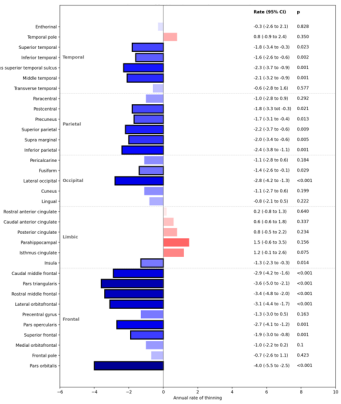

Figure 3. Annual rate of cortical thickness change for each region of interest according to Desikan–Killiany atlas.

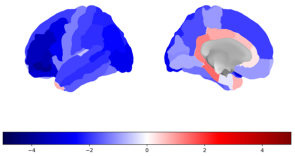

Figure 2. Annual rate of cortical thickness change mapped on the cortical surface using the Desikan–Killiany atlas, with color gradients indicating regional thinning rates across parcels.

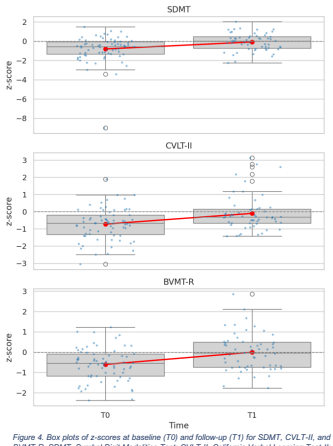

Figure 4. Box plots of z-scores at baseline (T0) and follow-up (T1) for SDMT, CVLT-II, and BVMT-R. SDMT, Symbol Digit Modalities Test; CVLT-II, California Verbal Learning Test-II; BVMT-R, Brief Visuospatial Memory Test- Revised.

CONCLUSIONS

In our cohort, treatment with OFA was associated with an improvement in cognitive performance, despite the observation of relatively high rates of brain atrophy and cortical thinning in patients with longer disease duration and older age.

Studies with longer follow-up and larger sample sizes are needed to further investigate these results.

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DISCLOSURES

The authors have nothing to disclose.

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