

Clinical Stability and Progression Define Distinct Brain Atrophy Trajectories in Ofatumumab-Treated Relapsing-Remitting Multiple Sclerosis

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INTRODUCTION

Brain atrophy reflects neurodegeneration in multiple sclerosis (MS) and is increasingly recognized as a clinically relevant outcome beyond inflammatory activity. While ofatumumab effectively reduces relapses and MRI activity, its impact on neurodegenerative processes and their relationship with clinical trajectories remains incompletely understood.

OBJECTIVES

To evaluate longitudinal patterns of brain volume changes in ofatumumab-treated relapsing-remitting MS (RRMS) and their association with distinct clinical trajectories, including stability and disability progression.

METHODS

Patients with RRMS treated with ofatumumab were analyzed over two years. Clinical measures included Expanded Disability Status Scale (EDSS), annualized relapse rate (ARR), and MRI activity (T2-weighted and gadolinium-enhancing [Gd+] lesions). Brain volumetry was performed using FreeSurfer. Analyses were conducted at the level of patient-years, stratified by clinical stability (stable vs progressing EDSS) and progression independent of relapse and MRI activity (PIRMA).

RESULTS

Eighty-two patients were included. Ofatumumab markedly reduced ARR (0.50 vs 0.06) and T2 lesion count (1.40 vs 0.08), with stable median EDSS (2.0). Overall, no significant global atrophy was observed. However, patient-year analysis revealed distinct patterns: clinically stable patient-years were associated with preservation or increase of cortical (0.53 vs -4.70), subcortical (0.04 vs -0.56), and total gray matter (-0.13 vs -3.77) volumes. In contrast, patient-years with disability progression showed consistent volumetric decline and increased white matter hypointensity (WM- hypo) accumulation (0.61 vs -0.04). Patients with PIRMA demonstrated greater gray matter loss (-0.85 vs -0.43) despite minimal inflammatory activity.

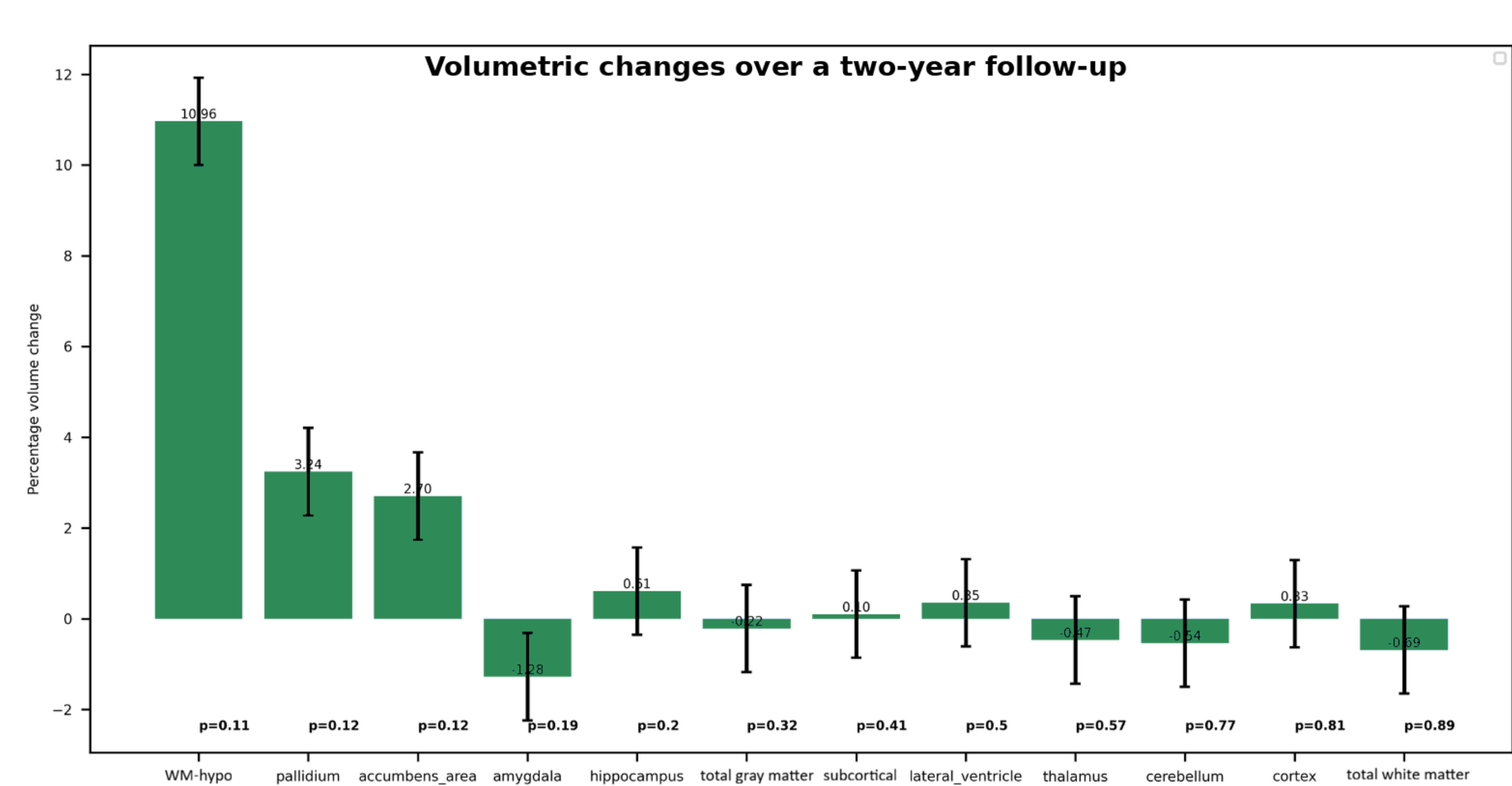


Figure 1. Mean percentage changes in MRI-derived brain-volume measures over the 2-year follow-up (n = 49). Values above or within the bars indicate mean changes; p values are shown below each brain structure. None of the observed changes reached statistical significance (all p ≥ 0.11).

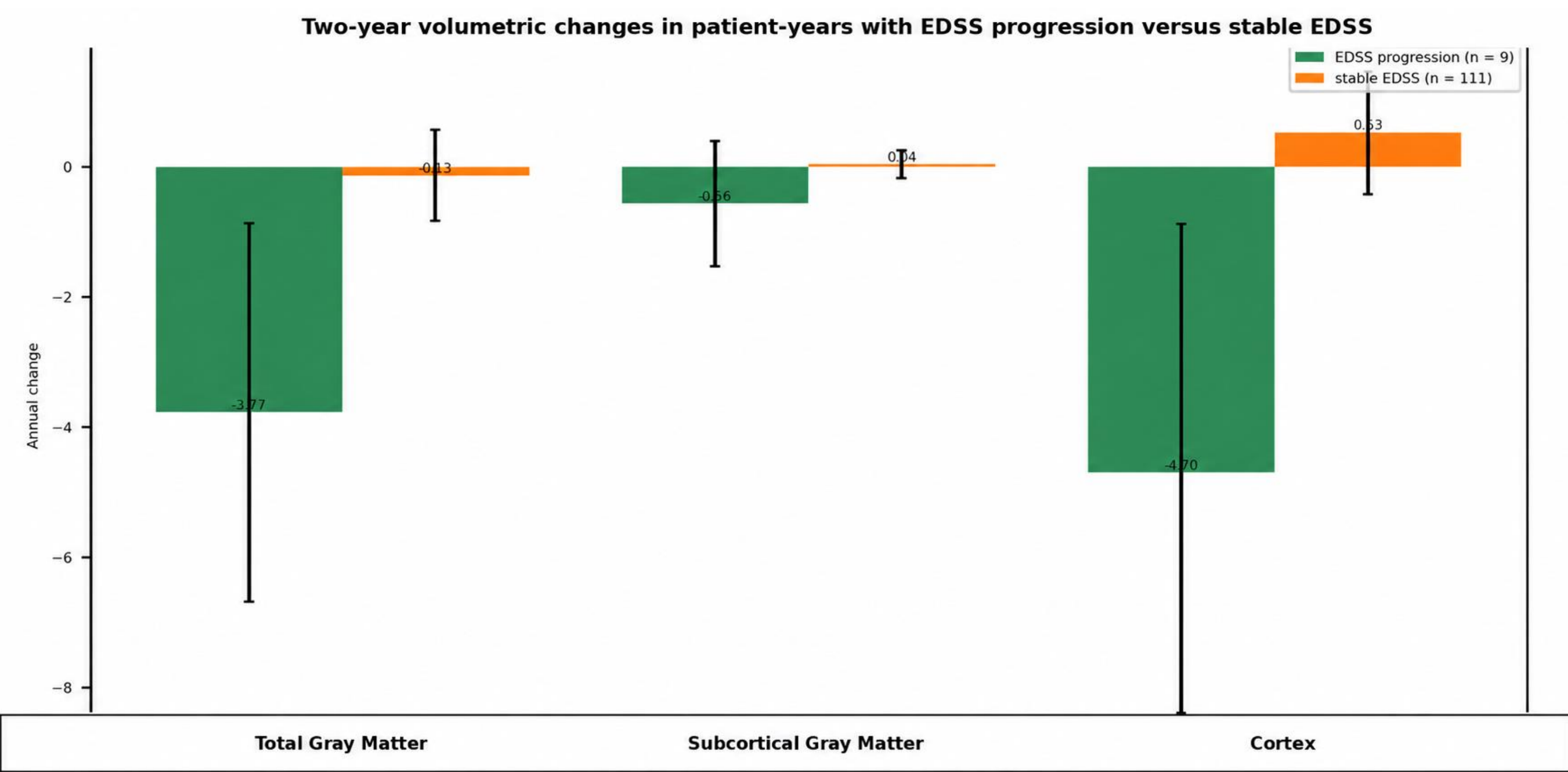


Figure 2. Mean orange bars represent patient-years with stable EDSS (n = 111). Values above or within the bars indicate mean changes. annual percentage changes in total gray matter, subcortical gray matter, and cortical volume over the 2-year follow-up, stratified by EDSS status. Green bars represent patient-years with EDSS progression (n = 9), and

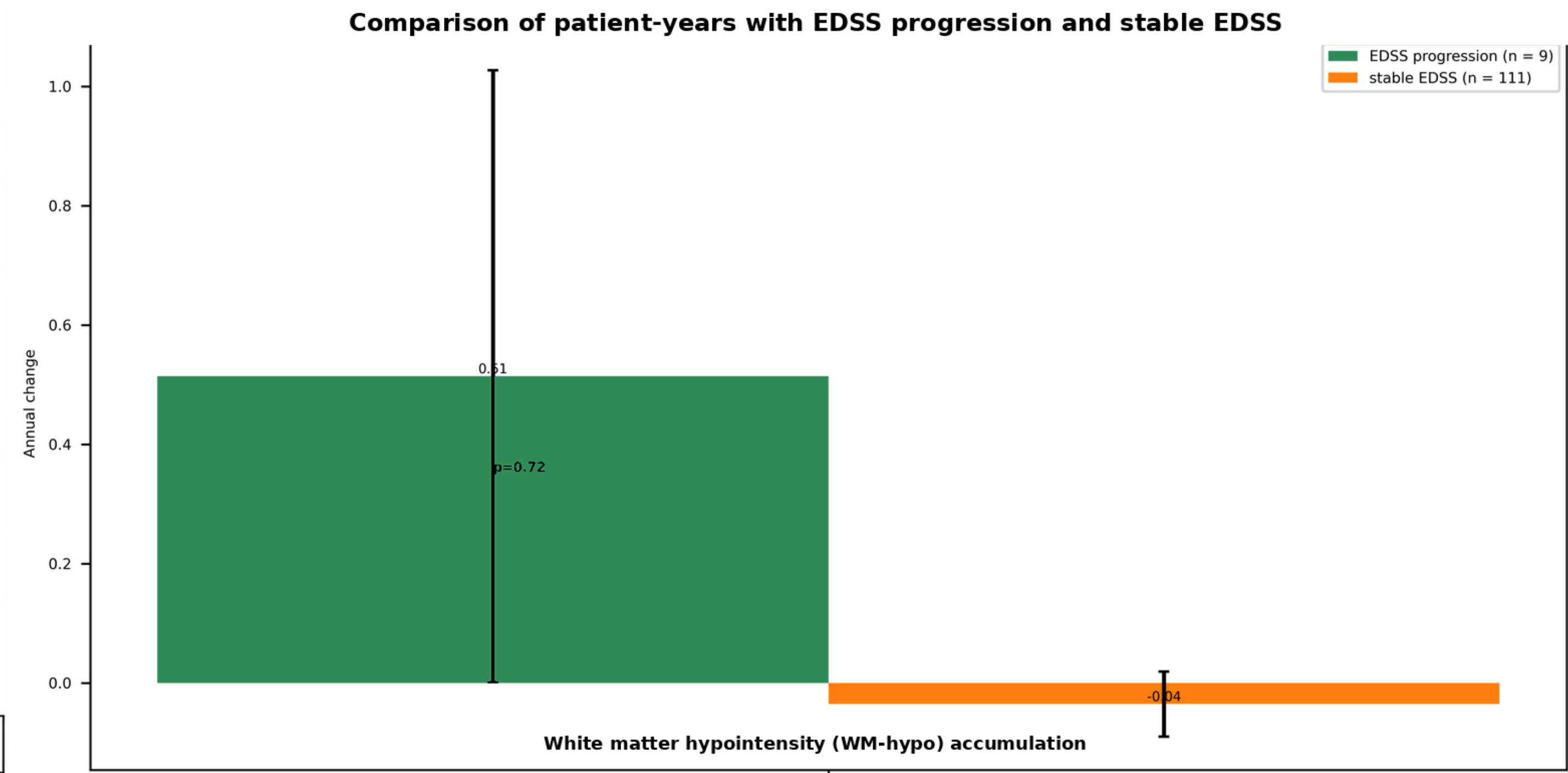


Figure 3. Mean annual change in white matter hypointensity (WM-hypo) volume in patient-years with EDSS progression (green; n = 9) and stable EDSS (orange; n = 111). The mean changes were 0.61 and -0.04, respectively; the between-group difference was not statistically significant (p = 0.72).

CONCLUSIONS

Brain atrophy dynamics under ofatumumab are strongly linked to clinical trajectories rather than inflammatory activity alone. Stability is associated with preserved gray matter volume, whereas progression—including PIRMA—is characterized by ongoing neurodegeneration despite inflammatory control. These findings highlight the value of longitudinal, patient-year-based analyses in capturing clinically relevant neurodegenerative processes in MS.

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