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Early Reduction in Plasma Glial Fibrillary Acidic Protein Levels in Siponimod-treated SPMS Patients (EXPAND) is Associated with Reduced Risk of Disability Worsening

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Abstract:

Background: In the EXPAND study, siponimod significantly reduced the risk of disability progression in patients with SPMS compared with placebo. Plasma glial fibrillary acidic protein (pGFAP) and plasma neurofilament light chain (pNfL) correlated with disease activity and have shown utility as markers of disability and treatment response in SPMS. The predictive value of the change in these blood biomarker levels during the early stage of treatment for disability worsening has not been investigated.

Objectives: To assess the predictive value of the change in pGFAP and pNfL levels from baseline (BL) to Month 3 (M3) for disability worsening in SPMS patients treated with siponimod or placebo.

Methods: In this post hoc analysis from the EXPAND core study, we quantified pGFAP and pNfL levels at BL and M3 in SPMS patients using Single Molecule Array technology. The relationship between changes in pGFAP and pNfL levels from BL to M3 (increase [≥0] vs decrease [<0]) and the time to 3-month confirmed disability worsening (3mCDW), time to 1-point sustained EDSS worsening and time to sustained EDSS 7.0 from M3 to end of study (EoS) was assessed. The impact of change in pGFAP levels was analyzed in patients with BL pGFAP >75 pg/mL (>10% quantile; independent from pNfL), and the impact of change in pNfL levels was analyzed in patients with BL pNfL >20 pg/mL (>15% quantile; independent from pGFAP) using Cox regression models adjusted for age, gender, disease duration at BL and relapses in the 24 months before study initiation, and EDSS score at M3. In these subsets of patients, analyses were conducted separately in the subgroups of patients treated with siponimod and placebo.

Results: Samples from 1453/1651 randomized patients were analyzed. In the patients treated with siponimod (pGFAP >75 pg/mL), a decrease in pGFAP levels from BL to M3 was associated with a reduced risk of disability worsening (hazard ratio [HR]: time to 1-point sustained EDSS worsening, 0.68 [p=0.0543]; time to 3mCDW, 0.66 [p=0.0053] and time to sustained EDSS 7.0, 0.79 [p=0.4470]) from M3 to EoS. In the patients on placebo, these associations were not observed (HR: time to 1-point sustained EDSS worsening, 1.19 [p=0.5193]; time to 3mCDW, 1.03 [p=0.8691]; time to sustained EDSS 7.0, 1.48 [p=0.3580]). Analyzing pNfL in the same way, a decrease in pNfL from BL to M3 was associated with only a slightly decreased risk of disability worsening in the siponimod treated patients (BL pNfL >20 pg/mL; HR: time to 1-point sustained EDSS worsening, 0.97 [p=0.8926]; time to 3mCDW, 0.91 [p=0.5249]; time to sustained EDSS 7.0, 0.64 [p=0.1610]). Unlike pGFAP, with pNfL similar trends were observed in the patients on placebo.

Conclusions: This is the first study that supports an association of the early lowering in pGFAP levels and a reduced risk of disability worsening in patients with progressive MS under disease modifying treatment. Results underscore the utility of pGFAP as treatment response and prognostic marker in SPMS.

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