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Reply to “Silent Progression or Bout Onset Progressive Multiple Sclerosis?”

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Reply to “Silent progression or bout-onset progressive multiple sclerosis?”

Response to letter to the editor by Gil-Perotin et al. (ANA-19-0481.R1)

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Gil-Perotin et al. ask if the relapsing patients we identified as having *silent progression* are identical to the previously described category *bout onset progressive MS* (BOPMS). The authors refer to an earlier paper by Paz Soldán et al. that uses the BOPMS term to refer to what is otherwise known as secondary progressive MS (SPMS). SPMS is recognized as progressive worsening independent from relapses after a relapsing disease onset. SPMS is typically recognized many years after disease onset and only after substantial disability has accumulated corresponding to expanded disability status scale (EDSS) scores of 4.0 to 6.0. In our recent publication, we found evidence of insidious worsening independent from relapsing activity (clinical or radiographic) in patients who were considered by their providers to still have relapsing remitting multiple sclerosis (RRMS). These silent progressors were not recognized as having SPMS (or “BOMPS” as Gil-Perotin et al. seem to prefer). The phenomenon of silent progression is more akin to the concept of “progression independent of relapse activity” (PIRA), as we referenced in our manuscript.[1]

The authors also raise an interesting question with respect to the long-term fate of persons living with MS: are there two groups of RRMS patients, one whose fate is to develop progression and a second who will not? Perhaps this is the case; however, it is more likely that larger numbers of patients with RRMS will be identified as having progression as the observation time lengthens and more sensitive indices of neurologic change are employed. For example, we and others have shown that combining EDSS with other measures such as cognitive function, walking speed, and upper limb function will increase the proportion of RRMS patients found to have relapse-independent progression. We agree with the authors that a common pathophysiology may well underlie silent progression and SPMS. The key point of our manuscript is that it is important to recognize silent progression during RRMS thereby prompting a therapeutic switch to treatments known to slow disability accumulation in patients with progressive MS.[2,3] Whether early escalation to high potency therapies, or their use at disease onset, prevents SPMS remains to be determined.

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Potential Conflicts of Interest

B.A.C.C. reports personal fees for consulting from Abbvie, Akili, Biogen, EMD Serono, GeNeuro, Novartis and Sanofi Genzyme, outside the submitted work. S.L.H. reports personal fees from Neurona (board of trustees), Symbiotix (scientific advisory board, SAB), Annexon (SAB), Bionure (SAB), Molecular Stethoscope (SAB) and Alector (SAB); non-financial support from F. Hoffmann-La Roche (travel reimbursement and writing assistance for CD20-related meetings and presentations), outside the submitted work.

References

1. Kappos L, Wolinsky JS, Giovannoni G, et al. Ocrelizumab reduces disability progression independent of relapse activity in patients with relapsing multiple sclerosis. P654. Paper presented at: ECTRIMS 2017; October 25–28, 2017; Paris, France.
2. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet. 2018;391:1263-1273.
3. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. N Engl J Med. 2017;376:209-220.