Response to Treatment According to Progressive Disease Type: Analysis from a Phase II Progressive MS Trial of Ibudilast

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Objective:
To report the effect of disease course (primary progressive vs secondary progressive) on the treatment effect of ibudilast in progressive MS.

Background: Despite recognition as different disease courses, primary progressive (PPMS) and secondary progressive (SPMS) are increasingly viewed as being more similar than different. Little is known about whether the two disease courses differ in treatment response. We evaluated the effect of ibudilast on the progression of brain atrophy according to disease course in a phase II clinical trial.

Design/Methods:
SPRINT-MS was a randomized, placebo-controlled 96-week phase II trial that evaluated the effect of ibudilast on brain measures of integrity in both PPMS (n=134) and SPMS (n=121) patients. Separate linear mixed models were used in PPMS and SPMS to evaluate rate of change in primary outcome (progression of brain atrophy) measured by brain parenchymal fraction (BPF). Baseline demographics and disease measures were included when appropriate.

Results:
Post-hoc analysis showed that there was a marginally significant three-way interaction between the treatment effect and disease course (p=0.0576). After further inspection, the overall treatment effect was primarily driven by patients with PPMS (p=0.005), and not by patients with SPMS (p=0.97). This difference may have been driven (at least in part) by faster atrophy progression in the PPMS placebo group compared to SPMS placebo (p=0.016). Although backwards selection (p<0.05) retained age, T2 lesion volume, RNFL, and longitudinal diffusivity as significant baseline covariates, the adjusted difference in treatment effect was still marginally significant (p=0.0715) and driven by PPMS (p=0.007).

Conclusions: The overall treatment effect of ibudilast on progression of brain atrophy in progressive MS appears to be driven by patients with PPMS, which may in part be because of their faster atrophy progression rates in untreated patients.