Effect of Ibudilast on Neurofilament-light Chain in Progressive MS: Analysis from a Phase II Trial

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Background

NfL is a candidate biomarker of treatment response in multiple sclerosis (MS) clinical trials. NfL was evaluated in several MS trials of anti-inflammatory therapies where the anti-inflammatory therapies were shown to decrease NfL levels. However, the utility of NfL as a biomarker in MS trials of non-anti-inflammatory therapies has not been reported previously.

Ibudilast is a small, brain-penetrating molecule that inhibits several cyclic nucleotide phophodiesterases, macrophage migration inhibitory factor, and toll-like receptor 4. In a phase II trial in relapsing MS, ibudilast did not decrease inflammation as measured by new MRI lesions, but was observed to reduce progression of brain atrophy in a dose-dependent fashion. This suggested that ibudilast may have a neuroprotective effect in the absence of an anti-inflammatory effect. This observation led to the SPRINT-MS trial, which was a two-year, 255-patient, randomized, placebo-controlled phase II trial of ibudilast in progressive MS. The SPRINT-MS found that ibudilast 80-100 mg/d was associated with a 48% slowing in progression of brain atrophy over two years. The SPRINT-MS trial provides an ideal setting to evaluate the performance of NfL.

Objective

To report the effect of ibudilast on serum and CSF neurofilament light (NfL) from the phase II trial of ibudilast in progressive MS.

Methods

Serum samples were collected at screening, 8, 48, and 96 weeks. In an optional sub-study, 75 patients consented to CSF sampling, which was collected at screening, 48, and 96 weeks. NfL was assayed using the SIMOA immunoassay. Analysis followed that of Kuhle, et al (Neurology 2019) using mixed model for repeated measurements with log(NfL) as the response variable and adjusted for treatment, age and log(baseline NfL) for serum NfL, and adjusted for treatment and age for CSF NfL. The model further included visit-by-treatment and visit-by-log (baseline NfL) interactions for serum NfL, and only visit-by-treatment interactions for CSF NfL, using an unstructured covariance matrix. Analysis was according to intent-to-treat (ITT) and included all available values in the statistical analysis.

Because active inflammation and other brain tissue injury can cause elevations of NfL and thus may confound efforts to measure the potential neuroprotective effects of a therapy, we conducted two post-hoc analyses in an effort to control for this confounding:

Censored Cohort 1 excluded time points

a) at or after onset of neurologic serious adverse events (SAE); or

b) within 6 months after a clinical relapse; or

c) when MRI showed any new or enlarging T2 lesions.

Since no MRI was obtained at week 8, all data from week 8 was excluded.

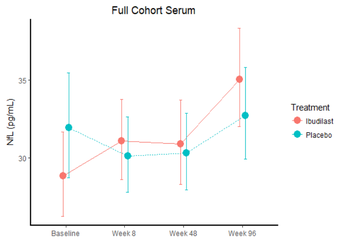
Censored Cohort 2 was the same as Cohort 1 except exclusion c) was relaxed to only exclude time points when MRI showed >3 new or enlarging T2 lesions.

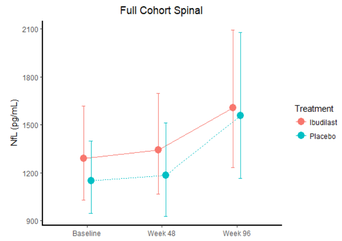
Results

Baseline NfL levels

	Serum		CSF	
	Placebo	Ibudilast	Placebo	Ibudilast
Full Cohort	31.9 n=120	28.9 n=119	1150.8 n=28	1290.3 n=30
Cohort 1	29.7 n=94	28.2 n=91	1086.2 n=26	1175.7 n=23
Cohort 2	30.7 n=105	27.7 n=103	1095.4 n=27	1275.2 n=28

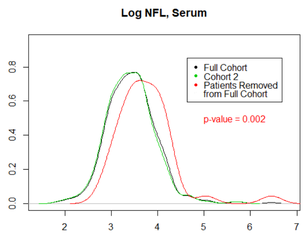
Full Cohort

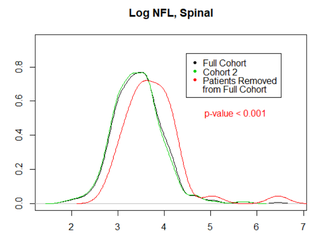




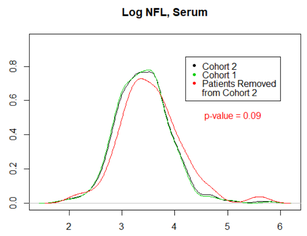
Over the course of the study, NfL increased in the overall study population (p<0.001). No between-group difference in NfL was observed in either serum (P=0.76) or CSF (P=0.46).

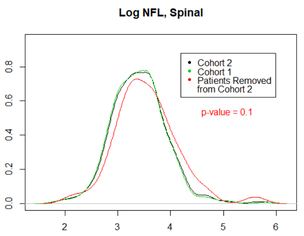
Censored Cohorts





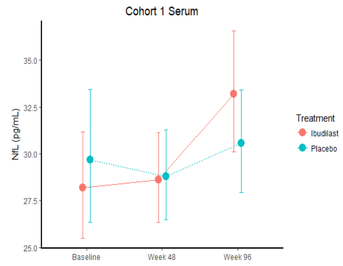
NfL from time points with either brain tissue injury from neurologic SAEs or inflammatory activity as measured by clinical relapse or new lesions on MRI had higher NfL in both serum and CSF.

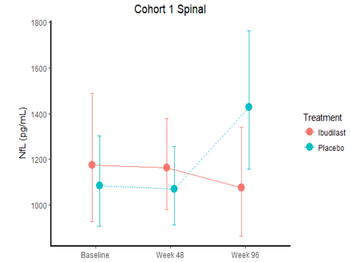


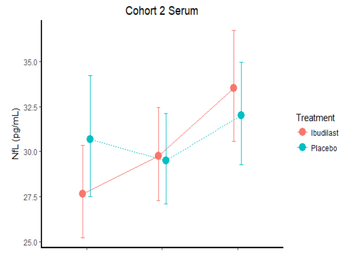


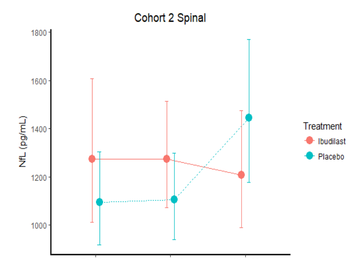
Comparison of the most restrictive censoring (any new/enlarging T2 lesions) to a less restrictive (>3 new/enlarging T2 lesions) found only modest advantage to the most restrictive censoring, but loss of 11% of subjects from both serum and CSF datasets (Table).

Censored Cohorts (cont.)









In neither Cohort 1 nor Cohort 2 was between-group difference in NfL observed in either serum (Cohort 1 p = 0.93; Cohort 2 p = 0.89) or CSF (Cohort 1 p = 0.48; Cohort 2 p = 0.24).

Conclusions

In a phase II trial in progressive MS, ibudilast treatment was not associated with a change in either serum or CSF NfL. CNS injury from serious adverse events, relapses, and new lesions on MRI were associated with increased neurofilament levels. Concurrent CNS injury may confound the use of NfL to measure potential neuroprotection from a non-anti-inflammatory therapy.

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