Respiratory function conservation in ALS is potentially linked to modulation of the innate immune system

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Abstract:

Objective: Neuvivo reanalyzed clinical data from the first phase 2 study of NP001, performed biomarker studies, and in accordance with FDA guidance published in 2019 defined a subgroup of patients that responded clinically to NP001. The objective of the current post hoc study was to test whether regulation of the innate immune system with NP001 would be associated with effects on respiratory vital capacity (VC).

Background: Recent studies have confirmed that inflammation associated with ALS pathogenesis begins at the neuromuscular junction (NMJ) and involves innate immune system activated macrophages derived from blood. VC measurements define the function of the NMJ between the phrenic nerve and the diaphragm, potentially linking innate immune function with a measurable, survival associated clinical outcome.

Design/Methods: To understand the role of the innate immune response in progressive VC loss we evaluated data derived from files reported to the FDA on the 6-month placebo controlled double blind phase 2A study of NP001 in ALS patients within three years of symptom onset (NCT01281631). Plasma specimens stored at -80C were used to evaluate components of the humoral innate immune system from patients who received 2 mg/kg NP001 or placebo. C reactive protein (CRP) of ≥1.13 mg/L, a prespecified plasma measure of inflammation, was used to define patient groups. as high or low CRP. Only patient records from those < 65 years of age who completed the six-month study and had plasma available were included.

Results: ALS demographic baseline values were similar between treated and controls. High CRP patients showed no age associated loss of VC whereas low CRP patients showed an age dependent loss of VC function. High CRP NP001 treated patients showed a 64% slower rate of VC decline compared with placebo and those with low CRP who showed no VC response. Plasma levels of serum amyloid A (SAA) were elevated in high CRP patients consistent with ongoing innate immune system activation. Plasma TGFB1, a dominant regulator of nuclear factor kappa B (NF-kB) in high CRP treated patients was 95% higher than placebo at 6-months confirming the activation and release of this anti-inflammatory factor by the innate immune alpha 2 macroglobulin (A2M) system.

Conclusions: This report is the first to link a therapeutic approach for controlling VC loss in ALS patients with biomarker confirmed regulation of the innate immune system.