Neurofilament Light Chain (NfL) as a Potential Biomarker in Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

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Introduction

Hereditary Transthyretin-Mediated (hATTR) Amyloidosis is a familial disease characterized by misfolding of the TTR protein, resulting in misfolding and aggregation of TTR that lead to the formation of amyloid deposits in multiple organs including the heart, liver, and peripheral nerves. hATTR amyloidosis is a progressive disease with limited treatment options. Patisiran is an RNAi therapeutic that has been approved for the treatment of hATTR amyloidosis. Patisiran is a 20-nt RNAi therapeutic that targets TTR mRNA, leading to the degradation of the mRNA and suppression of TTR protein production.

Methods

Data Analysis

• In a linear mixed model regression analysis for each protein determined if there was a significant differential time profile based on treatment.
• Principal component analysis was performed using Python’s sklearn package.

Objective

• Evaluate impact on circulating protein biomarkers in response to patisiran treatment in patients with hATTR amyloidosis with polyneuropathy.

Results

Multiple Plasma Proteins Differ Significantly Between Patisiran- and Placebo-Treated Patients (Figure 1)

• A significant change in levels over time was observed for 66 proteins following patisiran treatment (p<1.6 x 10^-10).
• NfL was identified as having the greatest significance (p=3.95 x 10^-12).

A significant decrease in N-terminal pro-brain type neurofilament light chain (NfL) to an RIA therapeutic was also measured (p=7.02 x 10^-12), consistent with the decrease in N-terminally processed NfL observed in the APOLO study.

PLASMA NfL IS INCREASED IN PATIENTS WITH hATTR AMYLOIDOSIS AND DECREASES WITH PATISIRAN TREATMENT

• Patients with hATTR amyloidosis with polyneuropathy had greater than 4-fold higher plasma NfL at baseline relative to healthy controls (Figure 2a: log scale).

Changes in NfL over time largely correlated with whether patients had a decrease or increase in their corresponding mNIS+7 (Figures 2b and 2c).

Effect of Disease Progression and Treatment on Overall Plasma Proteome Signature

• Probing each individual’s data for the two principal components (PC1 and PC2) reveals a separation between healthy controls and patients with hATTR amyloidosis with NfL at 18 months demonstrated a correlation of 0.40 (Figure 2d).

Figure 1. Proteins Identified to Have a Change Corresponding to Patisiran Treatment (Relative to Placebo) over 18 Months

Figure 2. Change over Time in NfL in Patients Treated with Patisiran and Placebo

Figure 3. Global Changes in Plasma Proteomes Observed with the Proteome of Patisiran-Treated Patients Trending Toward That of Healthy Controls at 18 Months

Conclusion

• NfL is a well-documented biomarker for neuroaxonal damage but limited research has been done thus far on its applicability in hATTR amyloidosis.

• Across >1000 unique proteins that were assessed from samples collected in the APOLO study, plasma levels of NfL had the most significant change in regards to patisiran treatment and were reduced following patisiran treatment at 9 and 18 months.
• NfL may serve as a biomarker of nerve damage and polyneuropathy due to TTR amyloid deposition.

• A correlation was seen between each patient’s change in polyneuropathy (as measured by mNIS+7) and change in NfL over 18 months, indicating that decreasing levels of NfL are associated with an improvement in polyneuropathy in the APOLO study.

• Patients treated with patisiran demonstrated a general shift in the proteome of patients toward that of healthy controls relative to placebo at 18 months.

• This study represents the most comprehensive plasma proteomics analysis in patients with hATTR amyloidosis to date and the first system-wide proteomics analysis of a hATTR amyloidosis human plasma.

• NfL offers the potential for earlier diagnosis of polyneuropathy in patients with hATTR amyloidosis and for monitoring disease progression and/or regression over time, with or without treatment.