Interaction (nonuniformity) of ALS progression and the efficacy of MN-166 (ibudilast)

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Introduction

Given the highly variable rate and form of disease progression among ALS patients (Watanabe et al 2016), the large dispersion of ALSFRS-R scores reported in clinical studies may contribute to the failure to achieve statistical significance in disease progression evaluation. MN-166 (ibudilast), a small molecule that inhibits selective phosphodiesterase subtypes (PDEs) and macrophage migration inhibitory factor (Mif), is in clinical development for the treatment of ALS.

Objective

We performed Stepwise regression analysis to identify the factors that have an impact on the treatment effect of MN-166 as assessed by the ALS score. We hypothesized that ALS disease history (time from first ALS symptom onset to trial enrollment) might have substantial effect on responsiveness to drugs.

Background

In the single-center, double-blind, placebo-controlled, clinical trial evaluating MN-166 in ALS patients (MN-166-ALS-1201), a total of 51 subjects (34 in the active group, 17 in the placebo group) without NI support were enrolled. There was a greater number of treatment responders (stabilized or improved ALSFRS-R score from baseline to end of 6 months treatment) in the MN-166 group than in the placebo group although this finding did not reach statistical significance. These results led us to investigate which background factors of patients’ characteristics reasonably predict both ALS disease progression and treatment efficacy.

MN-166-ALS-1201 trial Design

Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Placebo (N=17)</th>
<th>MN-166 (N=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57.5 years</td>
<td>53.2 years</td>
</tr>
<tr>
<td>Gender Male Female</td>
<td>12 (70.6%)</td>
<td>23 (67.6%)</td>
</tr>
<tr>
<td>Family History of ALS</td>
<td>2 (11.8%)</td>
<td>2 (5.9%)</td>
</tr>
<tr>
<td>Months from first onset</td>
<td>26.8 months</td>
<td>17.0 months</td>
</tr>
<tr>
<td>ALS History (months)</td>
<td>56 (94.1%)</td>
<td>25 (73.5%)</td>
</tr>
<tr>
<td>Baseline ALSFRS-R score</td>
<td>39.0</td>
<td>39.3</td>
</tr>
</tbody>
</table>

Overall, baseline characteristics between the MN-166 vs. placebo groups were generally similar. However, mean months since first symptom onset was shorter for the MN-166 vs placebo treatment groups, 17.9 vs 28.8 months.

Methods

Regression Tree Analysis and Multiple Regression Analysis were used to evaluate the potential factors that affect treatment effect. Evaluated factors were gender, age, race, site of onset (upper limb, lower limb, bulbar onset) UMN/LMN symptom involvement, and ALS history at trial enrollment (latency between trial enrollment and first ALS symptom).

Correlational Analysis was conducted to correlate the following:

1. ALS history and baseline ALSFRS-R score
2. ALS history and disease progression, measured as change in ALSFRS-R score from baseline to end of 6 month treatment

Results

Regression Tree Analysis

Regression Tree Analysis analyzes the impact on treatment effect by the combination of factors. It was suggested that site of onset (bulbar onset Yes or No) and ALS history (cut off days is 618 days on symptom) are the substantial factors that have an impact on treatment effect.

Red dot=placebo group  Blue dot =MN-166 group

Multiple Regression Analysis (Stepwise Regression)

Multiple Regression Analysis analyzes the impact on the overall drug effect of each factor. Stepwise Regression further narrowed down that gender, bulbar onset, LMN bulbar symptom and ALS history (i.e. days since first onset of symptom) are the factors affecting treatment effect.

Conclusions

• A significant negative correlation between higher baseline ALSFRS-R scores at enrollment and ALS history (time from first symptom to trial enrollment) was observed in short ALS history patients, but not in long ALS history patients.
• A significant correlation between ALS progression and ALS history was observed in the placebo group. However, it was found that this correlation was lost in the MN-166 group and was attributed to treatment effect in several short ALS history patients.
• Despite the study’s randomization design, there were meaningful differences found in ALS history and disease duration between the MN-166 and placebo groups at baseline. Plans are in place to mitigate the risk of this occurring again in the upcoming Phase 2b/3 study (NCT04057898)
• The efficacy of MN-166 is expected to be more robust in patients with a short ALS history.

“Bulbar onset” and “ALS history” (i.e. days from first onset of symptom) were identified as the factors that were statistically significant (p<0.05). Bulbar onset was considered as a “statistically important factor” and “ALSFRS-R score progression” was milder in the Bulbar onset group as determined by regression tree analysis.

Although it was not statistically significant, the p-value improved when focused on the subgroup with short ALS history. Taken together with the analysis results reported herein, patients with short ALS history might benefit more from MN-166 treatment than those with long ALS history.

Wilcoxon Rank-sum Test

The p-value was 0.254 with Exact test when limited to patients with ALS history ≤570 days. Although it was not statistically significant, the p-value improved when focused on the subgroup with short ALS history. Taken together with the analysis results reported herein, patients with short ALS history might benefit more from MN-166 treatment than those with long ALS history.