Evidence of Sustained Low Dose Bryostatin Efficacy for Treatment of Alzheimer's Disease: Consistency of Multiple Evaluation Analyses

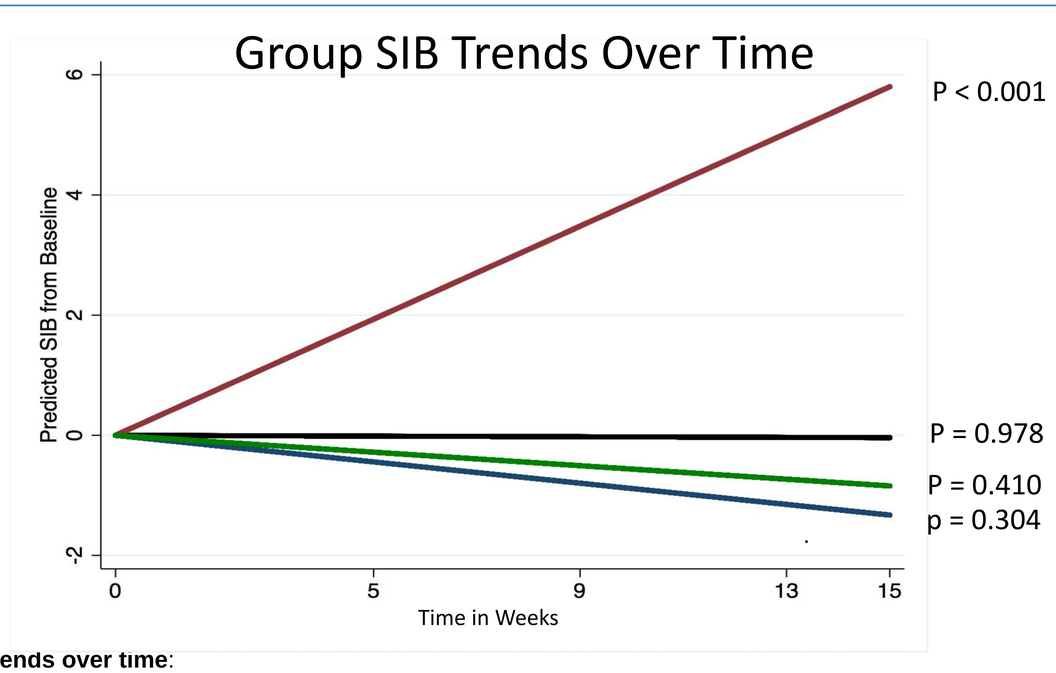
Elaine Grenier, BS; Richard Thompson PhD; LJ Wei, PhD; Daniel L Alkon, MD

Introduction

Neurotrope's Phase II trial of bryostatin-1 to treat moderate to severe Alzheimer's disease (AD) was an exploratory, multiple dose trial of a drug with novel mechanisms of action – synaptogenesis and anti-apoptosis. Bryostatin activates PKC epsilon, which regulates synaptogenic growth factors (e.g. BDNF,NGF, etc.), anti-apoptosis, degradation of A Beta oligomers, and reduction of neurofibrillary tangles.

Methods

This study was designed to explore safety and efficacy for the treatment of cognitive deficits in moderate to severe AD patients measured by changes in Severe Impairment Battery (SIB) scores. The initial 147 enrolled patients were evenly distributed among three arms (1:1:1): placebo (n=50 at start of trial, 42 completed), 20µg (n=49 at start of trial, 38 completed), 40µg (n=48 at start of trial, 33 completed). Each patient received 7 doses of either placebo or bryostatin-1 over 12 weeks. In a pre-specified exploratory analysis, the interaction of memantine as a concurrent, standard-of-care drug regimen was examined. The Full Analysis Set (mITT), as well as the Completer Analysis Set (CAS), were each pre-specified in the Statistical Analysis Plan (SAP) as alternative means to assess the primary, secondary, and exploratory efficacy endpoints for moderate to severe AD patients.



Group SIB trends over time:
Red = 20 µg bryostatin, in the absence of memantine
Black = placebo in the absence of memantine
Green = 20 µg bryostatin in the presence of memantine
Blue = placebo in the presence of memantine

MMRM was used in the trend analysis to provide consistency with the analysis of the whole patient sample. Based on the statistical trend analysis, only the 20 µg bryostatin in the absence of memantine group shows a significant positive SIB trend (e.g. SIB improving over time). The treatment-by-time interaction, indicating a difference in treatment effect by arm, was highly significant ($p < 0.001$). This significant positive trend indicates a treatment effect of bryostatin for this patient group only. These data further indicate that the patients in the memantine-free group improved throughout the 15 week protocol.

Results

Safety: The lower dosing protocol (24µg for the first two weeks, followed by 5 doses of 20µg every other week) demonstrated safety minimally different from the placebo protocol. The higher dose (48µg for the first two weeks, followed by 5 doses of 40µg every other week) patients showed reduced safety, and increased drop-out rates and was considered to correspond to higher doses measured in vitro that cause downregulation of PKC rather than activation.

Efficacy: The Completers showed evidence of improvement in the SIB at week 13 ($p < 0.070$), and evidence of improvement for the secondary endpoint of week 5 ($p < 0.016$). Furthermore, for a pre-specified exploratory endpoint at week 15, 30 days after completion of dosing, SIB improvement was at the $p < 0.029$ in the Completer group, providing evidence of sustained improvement up to 30 days post-dosing. The mITT group showed evidence of improvement at week 5. The 40µg cohort patients showed no efficacy, reduced safety, and increased drop-out rates.

Exploratory Analysis: A pre-specified exploratory analysis of the potential bryostatin-1 interaction with standard of care therapy (donepezil or memantine) was subjected to thorough statistical analyses (including a 2-sample t-test with unequal variance, a Wei and Lachin analysis, and a trend analysis). These analyses provided evidence of clinical improvement of bryostatin-1 in the absence of memantine for patients with moderate to severe AD. Patients on bryostatin-1 *in the absence of memantine* showed evidence of sustained SIB improvement over baseline compared to placebo (> 6.30 points). Individual patient trends over time revealed that 15 out of 16 patients (94%) in the 20µg bryostatin-1, non-memantine group showed improvement in SIB by the end of the trial.

Discussion

While the memantine interaction with bryostatin adds complexity to the potential benefit of bryostatin for AD patients, we would submit that it also provides some additional evidence for this potential benefit. Namely, an effect of bryostatin that occurred only by chance is not likely to be eliminated in only patients who received standard-of-care memantine.

The apparent persistence of the bryostatin-induced SIB improvement signals is consistent with a long-lasting consequence of PKC epsilon-growth factor effects that could induce the growth and/or maturation of synaptic networks in the brain. This might translate into long-lasting benefit in cognitive function.

Although the analyses of the primary endpoint at 13 weeks was not significant for the full data set (FAS), the data did provide evidence of bryostatin's improvement signals of the SIB scores at 13 weeks for the Completers Set - even 30 days after drug dosing completion. Pre-specified exploratory analyses, moreover, although implemented in a post-hoc framework, did provide evidence of significant benefit throughout the lower dose (20µg) protocol.

Conclusions

The consistency of these multiple analyses provided strong evidence of a treatment effect for the 20µg bryostatin-1 protocol in advanced AD patients in the absence of memantine. Figure: Model for Repeated Measures (MMRM) models with random intercepts.

Contact

Daniel L Alkon, MD
Neurotrope, Inc.
dalkon@neurotrope.com
website: www.neurotrope.com

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