**A Hope Summarized for Amyotrophic Lateral Sclerosis: Trial of Sodium Phenylbutyrate–Taurursodiol for Amyotrophic Lateral Sclerosis**

Rishika Sharma

251008648

MEDSCIEN9502

Dr. Martin Duennwald

Friday, October 18th, 2024

Interdisciplinary Medical Sciences

Schulich School of Medicine and Dentistry

Western University

**Assignment Acknowledgement**

This assignment used generative AI, specifically Grammarly, to check for grammatical correctness. This assignment has a Turnitin originality score of 6%.

**Assignment Knowledge Check**

|  |  |  |
| --- | --- | --- |
| **Student Name** | **What aspects of this assignment did you find less challenging?** | **What aspects of this assignment did you find more challenging?** |
| Rishika Sharma | 1. Understanding how to interpret the figures. 2. Making notes on the articles. 3. Creating a glossary for terms I was unaware of. | 1. Paraphrasing technical aspects of the articles. 2. Finding the articles. 3. Writing to ensure a balance of differet aspects. |

**Summary: Trial of Sodium Phenylbutyrate–Taurursodiol for Amyotrophic Lateral Sclerosis**

Protein aggregation and misfolding due to endoplasmic reticulum (ER) dysfunction or stress and/or mitochondrial dysfunction has been suggested in the pathogenesis of Amyotrophic lateral sclerosis (ALS).1,3 ALS is defined by degradation of motor neurons in the spinal cord and motor cortex that results in accelerating muscle weakness.4 Sodium phenylbutyrate and taurursodiol have been known to reduce the death of neurons. Sodium phenylbutyrate behaves as a molecular chaperone reducing toxicity ER-stress related toxicity, while taurursodiol decreases the mitochondrial permeability and enhances the cell’s apoptotic threshold.2,5 Hence, it is hypothesized that a combination of sodium phenylbutyrate-taurursodiol may reduce the rate of ALS progression through decreasing neurodegeneration.

This study is a Phase 2, multicenter, double-blind, randomized, placebo-controlled trial, which assesses the efficacy of a coformulation of sodium phenylbutyrate–taurursodiol in 137 adult participants with ALS.4 The participants must have experienced an onset of symptoms within a window of 18 months, have a slow vital capacity (SVC) higher than 60% of the expected value rooted in the participant’s sex, height and age and they cannot be using Riluzole at the beginning of the trial or 30 days before screening.4

Participants were randomly allocated in a 2:1 ratio to receive the combination intervention (89 participants), consisting of 3g of sodium phenylbutyrate and 1g of taurursodiol or the placebo (48 participants) through either oral administration or a feeding tube.4 Participants began with a single dose for the first three weeks, progressing to a dose in the morning and one in the evening for the remaining 21 weeks, for a total time of 24 weeks.4 Follow-up appointments were conducted every 3 weeks for 24 weeks, with a final visit at 28 weeks.4

The primary endpoint of the trial involves assessing the rate of decline using the ALS Functional Rating Scale-Revise (ALSFRS-R) over 24 weeks.4 Secondary endpoints were to evaluate tracheostomy, time to death, permanent ventilation and alterations in strength of muscles, plasma levels of phosphorylated neurofilament H levels, a related biomarker, and/or SVC.4 The study was powered at 80% to distinguish a 30% difference in the rate of decline in the ALSFRS-R complete score between the two intervention groups, with a two-sided alpha level of 0.1.4 Analysis of the primary endpoint unveiled that those receiving the combination therapy underwent a reduced rate of decline in ALFSR-R scores as compared to the placebo, with a difference of 0.42 points per month.4 However, there were no significant differences seen in the secondary endpoints.4

The trial was approved by IRBs at every center, there was informed consent given by every participant.4 There were certain adverse events that were experienced, such as diarrhea and nausea, which were mitigated with adjustments to the dosing regimen.4

Even though there were no significant observations made in the secondary outcomes, the reduction in the rate of functional decline seen in the assessment of primary outcomes warrants further research. This combination therapy can potentially be beneficial for those with ALS if administered with other agents, or earlier upon diagnosis. There needs to be more research surrounding the safety and efficacy profiles of this coformulation.

References:

1. Jaronen M, Goldsteins G, Koistinaho J. ER stress and unfolded protein response in

amyotrophic lateral sclerosis—a controversial role of protein disulphide

isomerase. Front Cell Neurosci. 2014;8:402. doi:10.3389/fncel.2014.00402.

1. Kaur B, Bhat A, Chakraborty R, et al. Proteomic profile of 4-PBA treated human

neuronal cells during ER stress. Mol Omics. 2018;14(1):53-63.

doi:10.1039/C7MO00054J.

1. Mehta AR, Walters R, Waldron FM, et al. Targeting mitochondrial dysfunction in

amyotrophic lateral sclerosis: A systematic review and meta-analysis. Brain

Commun. 2019;1(1). doi:10.1093/braincomms/fcz009.

1. Paganoni S, Macklin EA, Hendrix S, et al. Trial of Sodium Phenylbutyrate-

Taurursodiol for Amyotrophic Lateral Sclerosis. *N Engl J Med*.

2020;383(10):919-930. doi:10.1056/NEJMoa1916945

1. Rodrigues CM, Solá S, Sharpe JC, Moura JJ, Steer CJ. Tauroursodeoxycholic acid

prevents Bax-induced membrane perturbation and cytochrome C release in

isolated mitochondria. Biochemistry. 2003;42(10):3070-80.

doi:10.1021/bi0269904.