Proposed studies related to lipoic acid in multiple sclerosis

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1. Absorption and tolerability of racemic lipoic acid (LA) versus R-LA in progressive multiple sclerosis

Problem: The 1200mg daily dose of racemic lipoic acid (LA) found promising in the pilot clinical trial produced variable inter-subject peak levels at a single time-point and variable intra-subject levels between baseline and month 12 visits. Racemic LA was also difficult to swallow and produced stomach upset.

Goal: to improve absorption and tolerability of LA by using the R-LA form of LA.

Background: Lipoic acid (LA) in the natural form found in humans exists in the R chiral conformation (R-LA). Synthetic production of LA results in an even mix of R and S chiral conformations (termed “racemic LA”). There is conflicting literature regarding how well the R-LA and S-LA forms are absorbed. The pilot study of LA in secondary progressive multiple sclerosis (MS) found a reduction in brain atrophy among participants taking racemic LA, however there was stomach upset and the peak blood levels varied between participants and within the same participant at different visits. *Overall study hypothesis*: R-LA at a lower total dose will produce serum bioavailability results similar to racemic LA and do so with reduced variability and improved tolerability.

Study Aim 1: To determine the pharmacokinetic parameters of the R and S chiral components of racemic LA and of R-LA in people with progressive MS. *Hypothesis*: 600mg R-LA will produce similar serum bioavailability to the R chiral component of 120mmg racemic LA at baseline and at 3 months.

Study Aim 2: To evaluate the variability of the R-LA compared to racemic LA in people with progressive MS. *Hypothesis:* Inter and intra-subject variability (range and error) of bioavailability results produced by 600mg R-LA will be lower than the R chiral component of 1200mg racemic LA at baseline and at 3 months.

Study Aim 3: To evaluate the safety and tolerability of R-LA in people with progressive MS. *Hypothesis:* 600mg R-LA will be easier to swallow and have less stomach upset than 1200mg racemic LA.

Study plan: Blood levels of R-LA will be measured by Dr. Dennis Koop’s Bioanalytics laboratory (OHSU) on the first dose and at 3 months in 10 people with progressive MS taking 1200mg racemic LA daily and 10 people with progressive MS taking 600mg of the R-LA daily. Baseline and 3 month laboratory values will measure safety, and information regarding tolerability will be collected throughout the study period. Safety results will be tabulated and compared.

Future directions: If determined that the R-LA is preferentially absorbed and better tolerated than racemic LA, future studies will use this lower dose and better tolerated form of LA to determine if it is as effective in treating progressive MS as the racemic LA.

Timeline: 1 year

Budget: Research Coordinator (0.5 FTE) $25,000

PK studies $(est. $11,000)

Blood draws and bio-nutrition) $(est. $25,000)

Safety labs $2,550

Patient payments $3,650

Statistical analyses $(est. $8000)

Total $(est. $75,200)

1. Testing glutathione ratios as the mechanism of action of lipoic acid in progressive multiple sclerosis

Problem: The mechanism of action of lipoic acid (LA) that resulted in reduced brain atrophy in the pilot trial is unknown. Without understanding the mechanism, the potential to advance LA as a treatment in MS is limited.

Goal: To determine if the mechanism by which LA in secondary progressive MS is mediated through regeneration of the powerful antioxidant glutathione.

Background: LA is known to have multiple biological actions from laboratory studies, and it’s not clear which actions were responsible for the apparent benefits seen in the pilot trial that resulted in reduced brain atrophy in MS. Oxidative stress is considered to be a key driver of the neurodegeneration seen in progressive forms of MS. Glutathione is a powerful antioxidant found in animal cells capable of reducing oxidative stress, regulating iron metabolism, repair and synthesis of DNA and proteins, and determination of cell death. Glutathione exists in a reduced form (GSH) that can serve its beneficial effects and an oxidized form (GSSH) that itself can cause oxidative damage. Regenerating the reduced (beneficial) state of glutathione is a known action of LA and may be a mechanism by which it resulted in less brain atrophy (presumably by less cell death) in the pilot trial. To determine the effects of LA on glutathione, we will test ratios of reduced (GSH) to oxidized (GSSH) glutathione in serum stored from the pilot trial among participants prior to and after taking LA. We will then determine if the magnitude of change in the glutathione ratio, if found, correlates with the magnitude of effect on whole brain atrophy.

Study Aim 1: To quantify levels of GSH and GSSH and ratios of GSH:GSSH in stored blood from participants in the pilot trial prior to starting LA and after 3 and 12, and 24 months taking LA. *Hypothesis:* Levels and/or ratios favoring reduced glutathione will be increased in stored blood after taking LA.

Study Aim 2: To determine if the magnitude of glutathione ratio changes at month 12 or 24, if found in Aim 1, correlate with the magnitude of whole brain atrophy reduction found during the pilot study. *Hypothesis:* We expect a greater magnitude of change favoring reduced glutathione among participants who achieved greater reductions in whole brain atrophy.

Study plan: Stored serum from participants in the LA pilot trial will be sent to Dr. Daniel Linesman, University of Denver, who is experienced at analyzing glutathione. The results of reduced glutathione levels and ratios prior to and after taking LA for 3, 12, and 24 months will be analyzed for significant changes from baseline and between time-points. Glutathione ratio reductions at 12 and 24 months will be correlated with reductions in whole brain atrophy at month 24.

Future directions: If glutathione rations in the blood are positively influenced by LA, we will determine if glutathione ratio changes are also found in the brain among those taking LA. To do this, I would conduct a clinical trial during which people with progressive MS would undergo specialized brain MRI spectroscopy before and after taking LA to observe levels and ratios of glutathione. If changes are found, we would conclude that regeneration of glutathione is an important mechanism of action of LA in progressive MS. In addition, we would be able to use glutathione MRI spectroscopy as a biomarker, a way to measure the effectiveness of LA.

Timeline: 9 months-1 year

Budget: Research coordinator (0.2 FTE) $9,880

Laboratory testing $17,055

Statistical analysis $(est. $8000)

Total $(est. 34,935)