ID# NEURIMMINFL/2017/012757

Lipoic Acid Pharmacokinetics at Baseline and 1 year in Secondary Progressive Multiple Sclerosis

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Title: 95 characters

Word count: 743

References: 6

Tables: 0

Figures: 1

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Search terms: multiple sclerosis (41); All Clinical trials (19); lipoic acid; pharmacokinetics; secondary progressive

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Acknowledgements: Pure Encapsulations, Sudbury, MA, provided the lipoic acid and placebo.

Disclosures:

Dr. Frank Bittner reports no disclosures

Mr. Charles Murchison reports no disclosures.

Dr. Dennis Koop reports no disclosures

Dr. Dennis Bourdette reports no disclosures

Dr. Rebecca Spain reports no disclosures

Study funded by: Department of Veterans Affairs (B7493-W, R. Spain), National Institutes of Health (UL1TR000128).

Lipoic acid (LA) is a water and fat soluble oral anti-oxidant with anti-inflammatory properties. It has demonstrated benefit in animal models of multiple sclerosis (MS) and has been evaluated for MS relapse prevention and neuroprotection. However there are relatively few data regarding LA pharmacokinetics (PK) in elderly populations or with usebeyond four days. 1 Additionally, studies have used a variety of doses, a wide age range of subjects, and have measured, at times, specific enantiomers rather than the more commercially available racemic form. 2

Methods

Presented herein are PK results drawn at baseline and 1 year in the LA cohort of secondary progressive MS (SPMS) patients enrolled in a randomized placebo controlled trial of daily oral LA.. The study was approved by the Veterans Affairs Portland Health Care System & Oregon Health & Science University Institutional Review Boards**.** Patients arrived in the fasted state for the prior 10 hours, and a pre-dose sample was taken. Patients ate a meal immediately followed by 1200mg racemic LA (Pure Encapsulations, Sudbury, MA). Blood draws occurred at 30, 60, 90, 120, and 240 minutes post dose. Blood was allowed to clot at room temperature, serum separated by centrifugation, and stored at -80º Celsius until batch analysis by mass spectrometry.3

Non-compartmental analysis determined pertinent PK parameters including peak concentration (Cmax), time at peak concentration (Tmax), and observed bioavailability based on area-under-the-curve (AUC) using common pharmacodynamics calculations. Baseline and 1 year differences were assessed using mixed-models to account for serial correlation in the repeated measures and accommodate subjects with missing data at 1 year.

Results

Fifty-four patients were randomized in the parent trial, and of the 28 assigned to LA, 27 took at least 1 dose of LA and were included in PK analysis. Patients demonstrated 87% compliance by pill counts. Average age of the LA cohort was 57.9 (SD 6.7) years, 59% were female, and 96% Caucasian. Average disease duration was 30.9 (SD 9.3) years and median Expanded Disability Status Scale 5.5 (range 3.0 -8.0). Mean baseline Cmax was 14.9 ± 11.9 nmol/mL with a non-significant reduction at 1 year (11.3 ± 7.3, p=0.17, fig. 1a). At baseline, the largest proportion of subjects (13, 48%) had Cmax values at the 90 minute draw, whereas at year 1, the largest plurality (9, 41%) had a Cmax value at the 120 minute draw although this shift was not significant (p=0.47). There was a nonsignificant reduction in bioavailability at 1 year (AUC 1407 ± 873 nmol/mL vs 1116 ± 647 nmol/mL, p=0.10). Variability as measured by coefficient of variation (CV) was similar at baseline and 1 year (79.8% vs 64.9%) indicating stability in the PK measures., although the within-subject Cmax values at 30 minutes were often discrepant between years (158.5% and 179.4%, figure 1b). The patients (103, 114, 144, 147, and 155) terminating early (glomerulonephritis, MRI intolerance, prostate cancer, GI intolerance, and renal failure, respectively) did not have observably high Cmax levels.

Discussion

Patients overall maintained peak serum levels of daily oral LA, although there were non-significant reductions toward lower and later absorptions at 1 year. Cmax values occurred later (between 90 and 120 minutes) than a prior PK study of LA using the same dosing regimen (between 60 and 90 minutes).3 Due to limited clearance data, the analysis was unable to calculate many common, tail-based non-compartmental analysis parameters, including half-life. While mean Cmax values were similar between baseline and 1 year, visual observation demonstrates high between-subject variability for the same year, and within-subject variability between years based on the high coefficients of variation (CV>65%). Review of apparent outliers (115, 134, 137, 149) did not reveal underlying differences (e.g. age, weight, concomitant medications), nor were their mean brain atrophy rates different from the larger cohort. Breithaupt-Grögler et al (1999) also noted high between-individual variability in Cmax values of LA (99% and 96% of the measured R and S LA enantiomers at the highest dose of 600 milligrams of racemic LA). Reasons for between- and within- subject variable absorptions may be due to an elderly population with erratic gastrointestinal absorption, reduced hepatic perfusion, or drug-drug interactions. Alternatively, it may relate to intrinsic properties of LA or its delivery system.4,5,6 Yet unknown is if the PK variability and rapid clearance of LA impacts its therapeutic efficacy or has dosing implications for clinical trials or clinical use. Further development of LA may depend on improving its bioavailability and tolerability. This PK data represents the longest duration use of LA in an MS-specific population.

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Fig 1. Pharmacokinetic concentration versus time plots. (A) LA concentration at 6 time points over 120 minutes at baseline (n = 27) and 1 year (n = 22). Shown are means with standard deviation bars. (B) Individual traces of baseline and 1 year mean lipoic acid (LA) peak concentrations. Variability measured by the mean coefficient of variation across the pharmacokinetic trace was similar at the two time points (79.8% vs 64.9% respectively) with the highest variability found at 30 minutes (158.5% and 179.4% respectively).