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## LIPOIC ACID PHARMACOKINETICS AT BASELINE AND 1 YEAR IN SECONDARY PROGRESSIVE MS

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Lipoic acid (LA) is a water- and fat-soluble oral antioxidant with anti-inflammatory properties. It has demonstrated benefits in animal models of MS and has been evaluated for MS relapse prevention and neuroprotection. However, there are relatively a few data regarding LA pharmacokinetics (PK) in elderly populations or with use beyond 4 days.[1] In addition, 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 patients with secondary progressive MS enrolled in a randomized placebo-controlled trial of daily oral LA. The study was approved by the Veterans Affairs Portland Health Care System and Oregon Health & Science University Institutional Review Boards. Patients arrived after fasting for the prior 10 hours, and a predose sample was taken. Patients ate a meal immediately followed by 1,200 mg racemic LA (Pure Encapsulations, Sudbury, MA). Blood draws occurred at 30, 60, 90, 120, and 240 minutes after dose. Blood was allowed to clot at room temperature; serum was separated by centrifugation and stored at −80°C until batch analysis by mass spectrometry.[3]

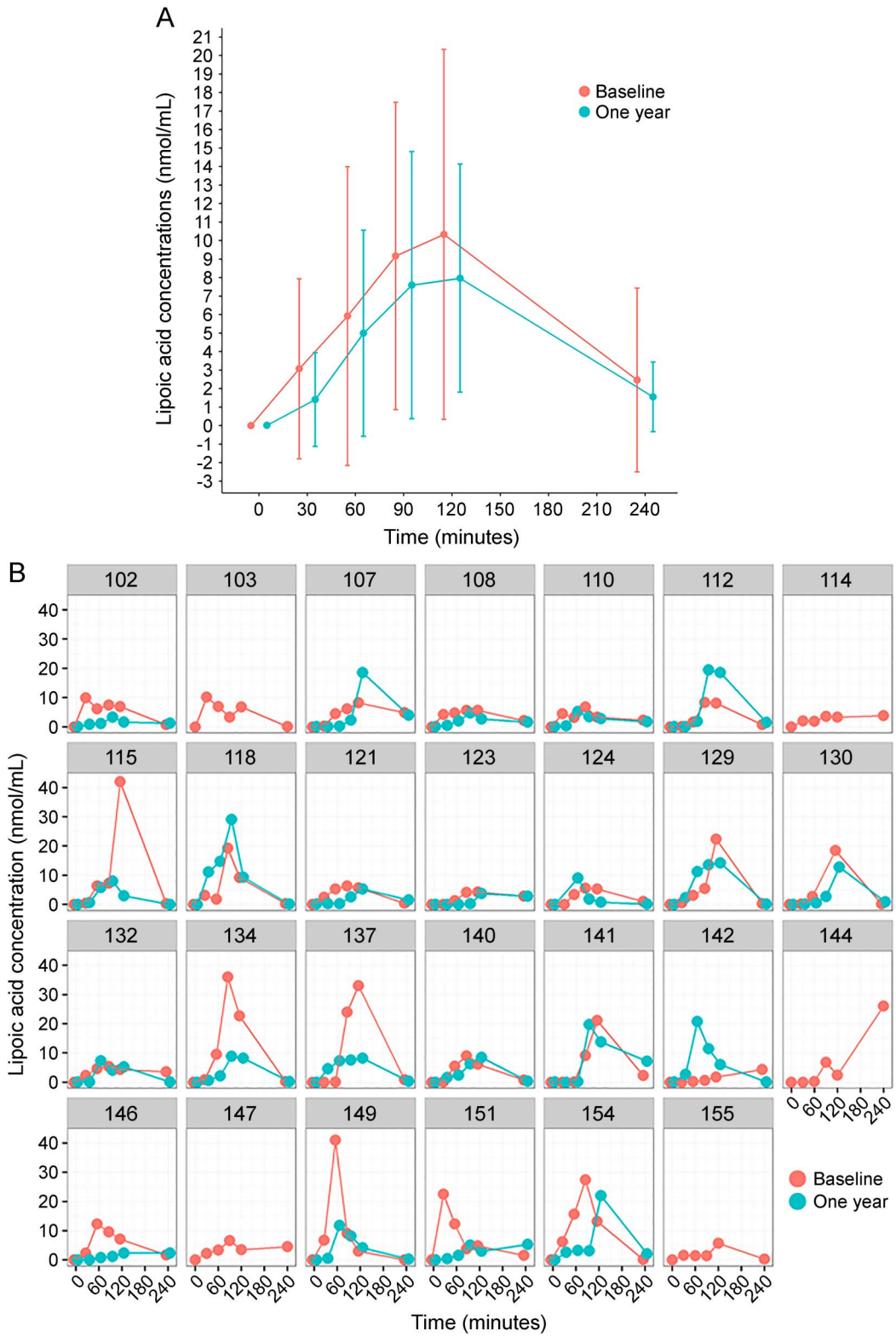
Noncompartmental analysis determined pertinent PK parameters, including peak concentration (Cmax), time at peak concentration (Tmax), and observed bioavailability based on area under the curve (AUC) using common pharmacodynamics calculations. Baseline and 1-year differences were assessed using mixed 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. The average age of the LA cohort was 57.9 (SD 6.7) years, 59% were women, and 96% were Caucasian. The average disease duration was 30.9 (SD 9.3) years, and the median Expanded Disability Status Scale score was 5.5 (range 3.0–8.0). The mean baseline Cmax was 14.9 ± 11.9 nmol/mL with a nonsignificant reduction at 1 year (11.3 ± 7.3, $p = 0.17$, figure, A). 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, B). The patients (103, 114, 144, 147, and 155) terminating early (glomerulonephritis, MRI intolerance, prostate cancer, gastrointestinal [GI] intolerance, and renal failure, respectively) did not have observably high Cmax levels.

**Discussion.** Overall, patients maintained peak serum levels of daily oral LA, although there were nonsignificant reductions toward lower and later absorptions at 1 year. Cmax values occurred later (between 90 and 120 minutes) than a previous PK study of LA using the same dosing regimen (between 60 and 90 minutes).[3] Because of limited clearance data, the analysis was unable to calculate many common, tail-based noncompartmental analysis parameters, including half-life. Although the 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%). A review of apparent outliers (115, 134, 137, and 149) did not reveal underlying differences (e.g., age, weight, and 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 mg of racemic LA). Reasons for between- and within-subject

**Figure** **Pharmacokinetic concentration vs time plots**




(A) LA concentration at 6 time points over 120 minutes at baseline (n = 27) and 1 year (n = 22). Shown are mean values with SD bars. (B) Individual traces of baseline and 1-year mean LA peak concentrations. Variability measured by the mean coefficient of variation across the pharmacokinetic trace was similar at the 2 time points (79.8% vs 64.9%, respectively) with the highest variability found at 30 minutes (158.5% and 179.4%, respectively). LA = lipoic acid.

variable absorptions may be due to an elderly population with erratic GI absorption, reduced hepatic perfusion, or drug-drug interactions. Alternatively, it may relate to intrinsic properties of LA or its delivery system.[4–6] 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. These PK data represent the longest duration use of LA in an MS-specific population.

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1. Teichert J, Hermann R, Ruus P, Preiss R. Plasma kinetics, metabolism, and urinary excretion of alpha-lipoic acid following oral administration in healthy volunteers. J Clin Pharmacol 2003;43:1257–1267.
2. Hermann R, Mungo J, Cnota P, Ziegler D. Enantiomer-selective pharmacokinetics, oral bioavailability, and sex effects of various alpha-lipoic acid dosage forms. Clin Pharmacol 2014;6:195–204.
3. Yadav V, Marracci G, Munar M, et al. Pharmacokinetic study of lipoic acid in multiple sclerosis: comparing mice and human pharmacokinetic parameters. Mult Scler 2010; 16:387–397.
4. Breithaupt-Grögler K, Niebch G, Schneider E, et al. Dose-proportionality of oral thioctic acid–coincidence of assessments via pooled plasma and individual data. Eur J Pharm Sci 1999;8:57–65.
5. Klotz U. Pharmacokinetics and drug metabolism in the elderly. Drug Metab Rev 2009;41:67–76.
6. Phua L, New L, Goh C, Neo A, Browne E, Chan E. Investigation of the drug-drug interaction between alpha-lipoic acid and valproate via mitochondrial beta-oxidation. Pharm Res 2008;25:2639–2649.