Efficacy and Safety of Antioxidant Treatment With α-Lipoic Acid Over 4 Years in Diabetic Polyneuropathy: The NATHAN 1 trial

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**Abstract**

To evaluate the efficacy and safety of α-lipoic acid (ALA) over 4 years in mild-to-moderate diabetic distal symmetric sensorimotor polyneuropathy (DSPN). **RESEARCH DESIGN AND METHODS** In a multicenter randomized double-blind parallel-group trial, 460 diabetic patients with mild-to-moderate DSPN were randomly assigned to oral treatment with 600 mg ALA once daily (n = 233) or placebo (n = 227) for 4 years. Primary end point was a composite score (Neuropathy Impairment...
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NATHAN 1 trial

Diabetic distal symmetric motor polyneuropathy (DSPN) chronic progressive disease accounts for one-third of the diabetes and increases the risk of bity, increased mortality, and...
be conducted for a minimum period of two Neurology Impairment (NIS) points (16,17). Therefore, we conducted the efficacy and safety of oral treatment with 600 mg ALA once daily for patients with mild-to-moderate DSPN.

**ARCH DESIGN AND 10DS**—The Neurological Assessment of Thiocystic Acid in Diabetic Neuropathy (ATHAN) 1 trial was a multicenter, randomized, placebo-controlled study with 600 mg ALA (Thiocystic HR; Meda, Bad Homburg, Germany) administered once daily or matching tablets with increased amounts of se and lactose that were identical in appearance in diabetic patients with moderate DSPN (18). The trial consisted of a 4-week screening phase, 6-week placebo-controlled phase, 4-year double-blind phase, and 4-week washout phase. All patients were obtained from the local ethics committees of all participating centers.

Inclusion criteria at the screening visit age 18–64 years; type 1 or type 2 diabetes mellitus; presence of stage 1 or 2 neuropathy according to the American Diabetes Association criteria (19); length of disease 1 year; absence of stage 1 or 2 neuropathy according to the American Diabetes Association criteria (19); statin regimen, weight, diet, and activity level as judged by the investigator; NIS—Lower Limbs and NIS—Upper Limbs scores of the reference population (corresponding to the percentile in the reference score population); NIS—Lower Limbs; NIS—Upper Limbs; one of the two abnormalities (i.e., abnormal nerve conduction attributes to two separate nerves ≥99th percentile for distal latency or ≤1st percentile for conduction velocity or ≥1st percentile for nerve conduction velocity or ≥2 abnormal heart rate during breathing (HRDB) ≤1st percentile total symptom score (TSS) in the

with the patient’s ability to participate in the trial; active neoplastic disease except for basal cell carcinoma; uncontrolled atrial fibrillation; clinically significant cardiac, pulmonary, gastrointestinal, hematologic, or other endocrine disease; organ transplants; aspartate aminotransferase or alanine aminotransferase >2 times normal; serum creatinine >1.8 and >1.6 mg/dL for men and women, respectively; drug or alcohol abuse within the last year; use of investigational drug within the last 6 months; severe or anaphylactic reaction to multiple drugs, sulfur products, or biologic products; ketoacidosis or hypoglycemia within the last 3 months resulting in hospital admission; antioxidant therapy (>400 IU vitamin E, >200 mg vitamin C, or >30 mg/day β-carotene) or pentoxyphylline within the last 3 months; history of use of medications or vitamins known to cause peripheral neuropathy including but not limited to use of phenytoin or carbamazepine ≥15 years or use of >100 mg/day pyridoxine within the last 12 months; and use of pain medications except for standard doses of salicylates, ibuprofen, indoles, fenamates, oxicoorm, or pyrazoles.

**Outcomes**

The primary outcome measure was a composite score including the NIS—LL+7 suggested by Dyck et al. (16) including 1) vibration detection threshold, 2) peroneal motor nerve conduction velocity (MNCV), 3) peroneal motor nerve distal latency, 4) peroneal compound muscle action potential (CMAP), 5) tibial motor nerve distal latency, 6) sural sensory nerve action potential amplitude, and 7) change in HRDB. The primary criterion of efficacy in the confirmatory analysis was the absolute change in the NIS—LL+7 score expressed as normal deviates (nfd from percentiles correcting for age and other applicable variables) between baseline (mean of visit during weeks 1 and 2 or last available visit) and 1 year, and is scored for each of the body (19). The NIS score (number, severity, and change) are from answers to 38 questions of weakness, questions 1–19; and autonomic, questions 30–38) (7). The trained, and certified physicians evaluated the NIS. Study physicians had passed training sessions and actual use of patients under observation of a formal certification process. Each has, quantitative sensory testing (QSTs), and autonomic testing was performed by trained and certified clinicians (P.A.L., W.J.L., P.J.D., and co.). All results were interactively entered on the Clinical and Quality Assurance System at Mayo Clinic and Health Eligibility, baseline conditions, and stimulus response patterns, and these were also assessed.

Safety measures included adverse events, vital signs, 12-lead resting electrocardiogram, X-ray at baseline, concomitant use of medications, and overall assessment of tolerance to physical examination. Laboratory including blood chemistry, behi
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The random allocation was balanced using an undisclosed block size. The investigators and the monitor used sealed envelopes to enable decoding of individual blinded treatment in an emergency.

**Results**

**Patient disposition, clinical characteristics, HbA1c, and vital signs**

The patient disposition throughout the trial according to the CONSORT Statement 2010 flow diagram (21) is shown. The demographic variables and measures at baseline in both groups are shown in Table 1. As a sign of homogeneity, no significant difference in any parameters listed except for HbA1c (0.0193).

Mean HbA1c decreased from 0.66 ± 0.14% in the ALA group to 0.48 ± 0.16% on placebo after 4 years. HbA1c declined with baseline by 0.62 ± 0.15% and by 0.60 ± 0.17% during 4 years of treatment with placebo (P = 0.9770). The corre
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Early vs. late intervention of high fat/low dose streptozotocin treated C57Bl/6J mice with enalapril, α-lipoic acid, menhaden oil or their combination: Effect on diabetic neuropathy related endpoints

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"...movement and prevention of progression of neuropathic impairments and was well tolerated (Ziegler et al., 2011). Menhaden oil is derived from the Menhaden, a forage fish of the genera Brevoortia Ethmidium that …"
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