Efficacy and Safety of Antioxidant Treatment With -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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Supplementary Data
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ficacy and Safety of Antioxidant eatment With α-Lipoic Acid Over Years in Diabetic Polyneuropathy

NATHAN 1 trial

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CTIVE—To evaluate the efficacy and safety of α-lipoic acid (ALA) over 4 years in mild-erate diabetic distal symmetric sensorimotor polyneuropathy (DSPN).

ARCH DESIGN AND METHODS—In a multicenter randomized double-blind -group trial, 460 diabetic patients with mild-to-moderate DSPN were randomly assigned reatment with 600 mg ALA once daily (n = 233) or placebo (n = 227) for 4 years. Primary nt was a composite score (Neuropathy Impairment Score [NIS]–Lower Limbs [NIS-LL] en neurophysiologic tests). Secondary outcome measures included NIS, NIS-LL, nerve con-, and quantitative sensory tests (QSTs).

LTS—Change in primary end point from baseline to 4 years showed no significant ce between treatment groups (P = 0.105). Change from baseline was significantly better A than placebo for NIS (P = 0.028), NIS-LL (P = 0.05), and NIS-LL muscular weakness e (P = 0.045). More patients showed a clinically meaningful improvement and fewer progression of NIS (P = 0.013) and NIS-LL (P = 0.025) with ALA than with placebo. onduction and QST results did not significantly worsen with placebo. Global assessment ment tolerability and discontinuations due to lack of tolerability did not differ between ups. The rates of serious adverse events were higher on ALA (38.1%) than on placebo).

LUSIONS—Four-year treatment with ALA in mild-to-moderate DSPN did not influ-e primary composite end point but resulted in a clinically meaningful improvement and ion of progression of neuropathic impairments and was well tolerated. Because the pri-mposite end point did not deteriorate significantly in placebo-treated subjects, secondary ion of its progression by ALA according to the trial design was not feasible.

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Diabetic distal symmetric motor polyneuropathy (DS chronic progressive disease around one-third of the diabetic tion and accounts for considera bidity, increased mortality, and

that the current strategies of intel betes therapy or multifactorial c cular risk intervention are not to slow the progression of DSP Thus, effective treatment of DSPN challenging for the physician (1,6)

Based on the pathogenetic me of DSPN, potential disease-m therapeutic approaches have be oped including antioxidants α-lipoic acid (ALA) (7–9) to dim creased oxidative stress (10). C tential modalities include th reductase inhibitors (11), growt (12), and the protein kinase C-β ruboxistaurin (13). These drugs h designed to favorably influence th lying pathophysiology of the rather than for symptomatic pa However, several problems have countered previously in designir priate clinical trials in DSPN. these, the most important are as 1) the lack of homogeneity of studied with respect to both the neuropathy and the degree of control; 2) different pathogene ways, the relative importance may vary intraindividually; 3) neuropathy that are too advance

be conducted for a minimum period
ars to achieve a clinically meaningful
: of two Neuropathy Impairment
(NIS) points (16,17). Therefore, we
d the efficacy and safety of oral
ent with 600 mg ALA once daily
l-to-moderate DSPN.

ARCH DESIGN AND IODS

—The Neurological Assess-
f Thioctic Acid in Diabetic Neurop-
(ATHAN) 1 trial was a multicenter
ters in the U.S., Canada, and Europe
ementary Materials]), randomized,
-blind, placebo-controlled, two-
:1 allocation ratio, parallel-group
trial using film-coated tablets con-
600 mg ALA (Thioctacid HR; MEDA
a, Bad Homburg, Germany) that
dministered once daily or matching
o tablets with increased amounts of
se and lactose that were identical in
ance in diabetic patients with mild-
lerate DSPN (18). The trial consisted
week screening phase, 6-week pla-
un-in phase, 4-year double-blind
and 4-week washout phase. Ap-
s were obtained from the local ethics
ttees of all participating centers.
clusion criteria at the screening visit
ge 18–64 years; type 1 or type 2
es defined by the American Diabe-
sociation criteria (1997); diabetes
on ≥1 year; presence of stage 1 or
N attributable to diabetes (18); sta-
sulin regimen, weight, diet, and
al activity level as judged by the in-
tor; NIS–Lower Limbs and seven
conduction tests (NIS-LL+7) score
th percentile (corresponding to
ansformed score points); NIS-LL
ints; one of two abnormalities [ei-
abnormal nerve conduction attri-
in two separate nerves ≥99th
tile for distal latency or ≤1st per-
for nerve conduction velocity or
ude or 2) abnormal heart rate dur-
ep breathing (HRDB) ≤1st percen-
total symptom score (TSS) in the

with the patient's ability to participate in the trial; active neoplastic disease except 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 month; γ-linolenic acid and ALA >50 mg/day 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, oxicams, 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 (nds from percentiles correcting for age and other applicable variables) between baseline (mean of visit during weeks 1 and 2 or last avail-

decrease in NIS or NIS-LL by ≥
respectively, while clinically m
progression was defined as an i
NIS or NIS-LL by ≥2 points, res
(16,17).

Duplicate measurements
measures within 1 week were p
at baseline, after 2 years, and afte
whereas single measurements
ried out at screening and after 6
1 year, and 3 years except for the
NSC, which were assessed as
sessments at screening and the
6-month intervals, and the TSS
inspection, assessed at 3-month

The NIS is the sum score
nations of muscle weakness, re

and great toe and is scored for b
of the body (19). The NSC scor
ber, severity, and change) are
from answers to 38 questions
weakness, questions 1–19; se
questions 20–29; and autonom
toms, questions 30–38) (7). Exp
trained, and certified (by P.J.D.
leagues) physicians evaluated the
NSC. Study physicians had par
in training sessions and actual
tion of patients under observati
a formal certification process. T
conduction, quantitative sens
(QSTs), and autonomic tests
formed by trained and certified p
(by P.A.L., W.J.L., P.J.D., and col
All results were interactively eva
the Reading and Quality Assura
ters (at Mayo Clinic and Health
Eligibility, baseline conditions, wa
stimulus response patterns, and t
were also assessed.

Safety measures included
ing of adverse events, vital signs
12-lead resting electrocardiogra
X-ray at baseline, concomitant
tion, global assessment of tolerab
physical examination. Laborat
including blood chemistry, her

a. The random allocation was bal- using an undisclosed block size The investigators and the monitor d sealed envelopes to enable decod- e individual blinded treatment in emergency.

tical analysis

matory analysis. The following nesis was tested: H0:μT = μP vs. ≠μP, where μT and μP denote an change in NIS-LL+7 tests from e to end point in the ALA and pla- groups, respectively. A two-way A including the factors treatment nter was performed. Variances were l to differ between treatments. De- f freedom were derived according ward-Rogers. A 95% CI for the treat- difference based on least squares stimates from the model without ctions was calculated. A second including treatment and center in- n was fitted explanatorily.

n analysis. An interim analysis erformed as soon as the 2-year most subjects were available. The ete table part of the study had been ed to and assessed by an indepen- pervisory committee. The decision tinuation of the study was based on nfirmatory test of the primary vari- t $P < 0.005$, the study would have topped. To ensure a global type 1 f 5%, the error level for the final s was set to $\alpha 2 = 0.0452$ according Šidák (20) inequality.

pending on the structure of data, contingency tables [*n* (%)] or de- ve statistics (*n*, mean, SD, median, quartiles) were presented for time s and changes from baseline. Sec- y end points were analyzed by ng a Wilcoxon Mann-Whitney test. verse events were coded according World Health Organization-Adverse ns Terminology (ART). Global in- es on preferred term and body class level were calculated based

size per group (*n*) were considered: SD 3.57, $n = 68$; SD 4, $n = 86$; SD 5, $n = 133$; SD 6, $n = 191$; SD 7, $n = 211$. To account for a relatively high dropout rate expected in this long-term study, randomization of 250 patients per arm was proposed. Analysis of the intention-to-treat population was primary for all efficacy variables. Homogeneity of baseline characteristics was investigated by exploratory statistical tests based on the intention-to-treat population on selected baseline variables.

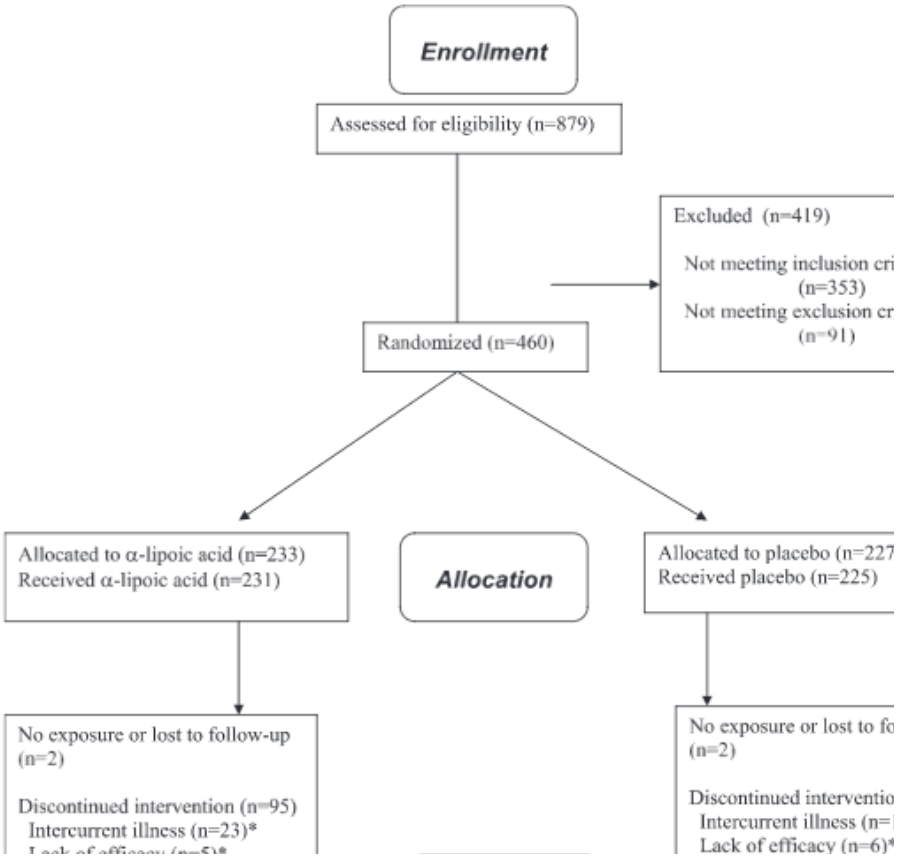
RESULTS

Patient disposition, clinical characteristics, HbA_{1c}, 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 gr shown in Table 1. As a sign of neity, no significant difference the groups were noted for any c rameters listed except for HR 0.0193).

Mean HbA_{1c} decreased from by 0.67 ± 1.41% in the ALA grou 0.48 ± 1.46% on placebo after After 4 years, HbA_{1c} declined c with baseline by 0.62 ± 1.59% and by 0.60 ± 1.78% during without significant differences the groups ($P = 0.9313$ after 4 yea 4 years, systolic blood pressure c

placebo ($P = 0.9770$). The corre



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*"...rovement 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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