Treatment of Symptomatic Diabetic Polyneuropathy With the Antioxidant α-Lipoic Acid

A 7-month multicenter randomized controlled trial (ALADIN III Study)

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OBJECTIVE — To evaluate the efficacy and safety of α-lipoic acid given intravenously, followed by oral treatment in type 2 diabetic patients with symptomatic polyneuropathy.

RESEARCH DESIGN AND METHODS — In a multicenter randomized double-blind placebo-controlled trial (Alpha-Lipoic Acid in Diabetic Neuropathy [ALADIN] III Study), 509 outpatients were randomly assigned to sequential treatment with 600 mg α-lipoic acid once daily intravenously for 3 weeks, followed by 600 mg α-lipoic acid three times a day orally for 6 months (A-A; *n* = 167); 600 mg α-lipoic acid once daily intravenously for 3 weeks, followed by placebo three times a day orally for 6 months (A-P; *n* = 174); and placebo once daily intravaneously for 3 weeks, followed by placebo three times a day orally for 6 months (P-P; *n* = 168). Outcome measures included the Total Symptom Score (TSS) for neuropathic symptoms (pain, burning, paresthesias, and numbness) in the feet, and the Neuropathy Impairment Score (NIS). Data analysis was based on the intention to treat.

RESULTS — No significant differences between the groups were noted for the demographic variables and the nerve function parameters at baseline. The TSS in the feet decreased from baseline to day 19 (median [range]) by −3.7 (−12.6 to 5.0) points in the group given α-lipoic acid intravenously and by −3.0 (−12.3 to 8.0) points in the placebo group (*P* = 0.447), but the area under curve on a daily basis was significantly smaller in the active as compared with the placebo group (85.6 [0–219] vs. 95.9 [5.5–220]); *P* = 0.033). After 7 months, the changes in the TSS from baseline were not significantly different between the three groups studied, which could be due to increasing intercenter variability in the TSS during the trial. The NIS decreased after 19 days by −4.34 ± 0.35 points (mean ± SEM) in A-A and A-P and −3.49 ± 0.58 points in P-P (*P* = 0.02 for α-lipoic acid versus placebo) and after 7 months by −5.82 ± 0.73 points in A-A, −5.76 ± 0.69 points in A-P, and −4.37 ± 0.83 points in P-P (*P* = 0.09 for A-A vs. P-P). The rates of adverse events were not different between the groups throughout the study.

CONCLUSIONS — These findings indicate that a 3-week intravenous treatment with α-lipoic acid, followed by a 6-month oral treatment, had no effect on neuropathic symptoms distinguishable from placebo to a clinically meaningful degree, possibly due to increasing intercenter variability in symptom scoring during the study. However, this treatment was associated with a favorable effect on neuropathic deficits without causing significant adverse reactions. Long-term trials that focus on neuropathic deficits rather than symptoms as the primary criterion of efficacy are needed to see whether oral treatment with α-lipoic acid over several years may slow or reverse the progression of diabetic neuropathy.

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Diabetic polyneuropathy leads to substantial morbidity; it is encountered in more than one-third of diabetic patients (1) and is associated with increased mortality in relation to its severity (2) and complications, such as foot ulcers (3). Because two pivotal landmark trials have demonstrated that intensive blood glucose control decreases the risk of microvascular complications and neuropathy in both type 1 and type 2 diabetic subjects (4,5), near-normoglycemia is now generally accepted as the primary approach to prevent diabetic neuropathy. However, these studies were not primarily designed to evaluate the effects of near-normoglycemia on diabetic neuropathy, nor did they include adequate numbers of patients with neuropathy. Thus, whether the progression of symptomatic peripheral neuropathy may be favorably influenced by any intervention remains to be established in controlled clinical trials (6), but prospective observational studies have shown that in advanced stages of neuropathy, several years of near-normal

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Abbreviations: A-A, α-lipoic acid followed by α-lipoic acid; ALADIN, Alpha-Lipoic Acid in Diabetic Neuropathy; A-P, α-lipoic acid followed by placebo; AUC, area under the curve; CV, coefficient of variation; DEKAN, Deutsche Kardiale Autonome Neuropathie; HRV, heart-rate variability; NIS, Neuropathy Impairment Score; NIS(LL), Neuropathy Impairment Score for the Lower Limbs; P-P, placebo followed by placebo; TSS, Total Symptom Score.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

glycemic control may be needed to observe beneficial effects on nerve dysfunction (7,8).

A variety of experimental studies have provided new insights into the putative mechanisms implicated in the pathogenesis of diabetic neuropathy (9,10). Several potential forms of treatment based on these pathogenetic considerations have been developed (9–14), some of which have been investigated in clinical trials of diabetic neuropathy. However, they either have shown inconclusive results (6,11,15), were hampered by methodological drawbacks (16,17), or used compounds associated with serious adverse reactions (18). Because the majority of diabetic patients at present will presumably not achieve near-normoglycemia, the advantage of these treatments may eventually be that they are effective despite the presence of hyperglycemia.

A growing body of evidence suggests that oxidative stress resulting from enhanced free-radical formation and/or defects in antioxidant defense is implicated in the pathogenesis of diabetic neuropathy by inducing neurovascular defects that result in endoneurial hypoxia and subsequent nerve dysfunction (13). Administration of physiological antioxidants, including α-lipoic acid, resulted in prevention of the neurovascular abnormalities associated with experimental diabetic neuropathy (19–23). A recent dose-finding clinical trial (the Alpha-Lipoic Acid in Diabetic Neuropathy [ALADIN] III Study) has demonstrated that intravenous treatment with α-lipoic acid (600 mg/day) for 3 weeks ameliorates the major neuropathic symptoms, such as pain, paresthesias, and numbness in type 2 diabetic patients with polyneuropathy (24). In a second controlled trial (Deutsche Kardiale Autonome Neuropathie [DEKAN] Study), an improvement in heart-rate variability (HRV) was found after 4 months of oral treatment with α-lipoic acid (800 mg/day) in type 2 diabetic patients with cardiac autonomic neuropathy (25). The present multicenter double-blind placebo-controlled trial was designed to assess the efficacy and safety of a sequential intravenous/oral treatment approach in three parallel groups of type 2 diabetic outpatients with symptomatic peripheral neuropathy who were randomly assigned to a 3-week treatment with α-lipoic acid (600 mg intravaneously) followed by 6-month oral treatment (600 mg three times a day); α-lipoic acid intravenously followed by placebo orally; or placebo intravenously and thereafter orally.

RESEARCH DESIGN AND METHODS

Protocol

The ALADIN III Study was a randomized double-blind placebo-controlled trial using the trometamol salt solution and tablets containing 600 mg of α-lipoic acid (Thioctacid T, Thioctacid, ASTA Medica, Frankfurt am Main, Germany) or placebo in three parallel treatment groups of type 2 diabetic outpatients with symptomatic peripheral neuropathy. Patients were randomly assigned to treatment with 600 mg α-lipoic acid once daily intravenously for 3 weeks, followed by 600 mg α-lipoic acid three times a day orally for 6 months (A-A); 600 mg α-lipoic acid once daily intravenously for 3 weeks, followed by placebo three times a day orally for 6 months (A-P); and placebo once daily intravaneously for 3 weeks, followed by placebo three times a day orally for 6 months (P-P). Intravenous infusion of 600 mg or placebo in 250 ml 0.9% isotone saline solution over 30 min once daily was administered over two periods of 5 days (Monday to Friday) and one period of 4 days (Monday to Thursday) during 3 consecutive weeks.

After approval by the Ethical Committee of the Landesärztekammer Hessen, Frankfurt am Main, Germany, and after written informed consent had been obtained, 516 patients were recruited from 71 outpatient centers in Germany. Twenty centers included ≥10 patients; 23 centers contributed with 5–9 patients; and 28 centers recruited <5 patients each.

Patients were eligible if they were 18–65 years of age, had type 2 diabetes according to the proposals of the National Diabetes Data Group (26), were treated with diet, oral antidiabetic agents and/or insulin, had stable glycemic control according to the investigator's judgment over 3 months before entry into the study, and had evidence of symptomatic symmetrical distal neuropathy (stage 2), i.e., Total Symptom Score (TSS) ≥4 points and Neuropathy Impairment Score (NIS) ≥2 points. Exclusion criteria were the following: *1*) asymmetrical neuropathy of the trunk and proximal lower limbs, *2*) presence of foot ulcers, *3*) peripheral vascular disease (nonpalpable foot pulses, intermittent claudication), *4*) myopathy, *5*) causes of neuropathy other than diabetes and significant neurological diseases, *6*) participation in a study of any investigational drug for neuropathy within the 3 months before the study, *7*) use of antioxidants or vitamin B within 1 month before the study, *8*) severe concomitant diseases, and *9*) pregnancy, lactation, or childbearing age without birth control devices.

The clinical characteristics at baseline of the three groups based on the intention to treat are shown in Table 1. As a sign of homogeneity of the groups formed by the randomization process, no significant differences between them were noted for any of the variables listed.

Outcome measures

TSS. At baseline (day 1) and each visit (days 2–5, 8–12, and 15–19) before infusion and after 6 months of oral treatment, neuropathic symptoms in the foot (pain, burning, paresthesias, and numbness) were scored by the physician or a trained nurse regarding their intensity as described previously (23). The comparison of the changes from baseline to day 19 in the TSS, ranging from 0 (no symptoms) to a maximum of 14.64 points (all symptoms are severe and [almost] continuously present), between the groups receiving α-lipoic acid and placebo, was used as the primary outcome measure.

NIS. The NIS was completed according to Dyck et al. (27) at baseline, day 19, and after 6 months of oral treatment by the physicians who had been trained before the start of the trial by an experienced neurologist (R.M.). A standard group of muscles was evaluated for weakness and muscle stretch reflexes (biceps, triceps, brachioradialis, knee, ankle). Perceptions to touch-pressure, vibration (128 Hz tuning fork), joint position, and pinprick perceptions were graded on the index finger and the great toe as normal (0), decreased (1), or absent (2). For evaluation of the NIS of the lower limbs (NIS[LL]), only neurologic abnormalities of that part of the body were tallied (27).

The comparison of the changes from baseline to day 19 in the TSS between the groups receiving α-lipoic acid and placebo was defined as the primary confirmatory criterion of efficacy. For analysis of the intravenous treatment period, the two groups given α-lipoic acid were summarized to one group (n = 338). Assuming an a priori treatment difference of 1.0 between α-lipoic acid and placebo for the changes in the TSS from baseline to day 19 and a standard deviation of s = 3.5, the required number of patients was estimated at n = 388 for the group given α-lipoic acid and n = 194 for the placebo group, with $\alpha = 0.05$ and $\beta = 0.1$ for the two-tailed t test. Com-

Table 1—*Clinical characteristics at baseline of the three groups studied*

	A-A	A-P	P-P
n	165	173	165
Sex (%)			
Male	45.5	54.3	50.3
Female	54.5	45.7	49.7
Age (years)	56.5 ± 7.1	57.0 ± 6.2	57.3 ± 5.5
BMI (kg/m²)	29.0 ± 4.8	28.8 ± 4.2	29.5 ± 4.8
Heart rate (bpm)	78.4 ± 8.8	78.1 ± 9.5	77.3 ± 9.6
Systolic blood pressure (mmHg)	141 ± 17	142 ± 14	140 ± 15
Diastolic blood pressure (mmHg)	82.7 ± 8.9	83.4 ± 8.0	81.5 ± 9.2
Duration of diabetes (years)	11.5 ± 8.4	11.7 ± 7.9	11.3 ± 7.7
Duration of neuropathy (months)	37.7 ± 38.5	35.1 ± 31.3	38.0 ± 36.7
HbA_{1c} (%)	8.5 ± 1.9	8.7 ± 1.8	8.7 ± 1.8
Insulin treatment	62.4	63.6	61.2
Smokers	15.2	16.8	13.3
Retinopathy	28.2	30.4	33.5
TSS	8.1 ± 3.0	8.3 ± 2.9	8.4 ± 3.2
NIS	14.0 ± 10.5	14.3 ± 10.5	14.0 ± 10.4
NIS(LL)	11.0 ± 7.0	11.3 ± 7.4	11.0 ± 7.3

Data are *n*, means ± SD, or % of patients.

parative analyses were performed on an intention-to-treat basis.

Assignment

Each patient was randomized according to his or her entry sequence following a central computerized randomization list.

Masking (blinding)

During the intravenous phase, ampules containing 10 ml (250 mg) and 4 ml (100 mg) of α-lipoic acid or placebo were used. Each patient received six ampules (four ampules with 10 ml each and two ampules with 4 ml each). Because of the yellow color of the α-lipoic acid containing solution, riboflavin (0.00375 mg/ml) was added to placebo to obtain preparations that looked alike. During the oral phase, tablets containing 600 mg α-lipoic acid or placebo of identical size, appearance, and taste were used. All investigators and participants were blinded to the randomization of the study drug assignments.

Laboratory methods

Glycosylated hemoglobin (HbA_{1c}) was determined at baseline, day 19, and after 3 and 6 months of oral treatment with the high-performance liquid chromatography technique using a Diamat analyzing system (Bio-Rad, Munich, Germany). The normal range is <6.3% of total hemoglobin.

Safety parameters were determined at baseline, day 19, and after 3 and 6 months of oral treatment. They included liver enzymes, creatinine, hemoglobin, full blood count, total protein, bilirubin, uric acid, cholesterol, and triglycerides. Treatment emergent adverse events were classified on the basis of the body systems using World Health Organization preferred terms.

Statistical analysis

The continuous data listed in Table 1 are expressed by the arithmetical means ± SD. The efficacy of the randomization process in balancing the groups with regard to the variables presented in Table 1 was analyzed using Fisher's exact test for categorical data and analysis of variance for continuous data. *P* values <0.1 were considered as a sign of inhomogeneity. The data from follow-up are given as the differences from baseline and are expressed as the arithmetical mean ± SEM, median (range), or as area under the curve (AUC) for the TSS at days 2–5, 8–12, and 15–19 during intravenous treatment. The AUC was computed exploratively in a post-hoc analysis using the formula

$$AUC = \tfrac{1}{2} \Sigma\, (t_{i+1} - t_i) \cdot (y_i - y_{i+1})$$

with $n+1$ measurements y_i at the time points t_i ($i = 0,\ldots,n$). Differences between groups were analyzed using the *t* test for two independent samples or the Mann-Whitney *U* test. Qualitative data are given as relative frequencies that were analyzed using the Fisher's exact test. The intercenter variability for the TSS and NIS was described by the coefficient of variation (CV). In this analysis, centers that included <10 patients were combined into one group. The level of significance was set uniformly at $\alpha = 0.05$.

RESULTS

Participant flow and follow-up

Among the 516 patients randomized, 509 were exposed to treatment and used for safety analysis, while 7 patients from one center were not exposed because of the inability of the investigator to proceed with the study. In 6 additional patients, no efficacy data were available, so that 503 patients were included in the intention-to-treat analysis (A-A: *n* = 165; A-P: *n* = 173; P-P: *n* = 165).

There were 34 (11/13/10) dropouts during the intravenous treatment period and an additional 92 (32/32/28) dropouts during oral treatment, i.e., the percentages of dropouts were 6.7 and 18.3% during intravenous and oral treatment, respectively, which resulted in a total rate of withdrawals of 25.0% throughout the trial, without significant differences between the three groups studied. Reasons for withdrawal (multiple entries possible) during the intravenous treatment period included lack of efficacy in 2 (1/1/0), drug intolerance in 2 (0/0/2), intercurrent disease in 6 (1/1/4), exclusion criteria in 19 (7/7/5), noncompliance in 5 (1/4/0), and other reasons in 7 (2/3/2) patients. Reasons for withdrawal during the oral phase were lack of efficacy in 24 (8/11/5), drug intolerance in 9 (4/1/4), intercurrent disease in 15 (4/5/6), exclusion criteria in 11 (3/6/2), noncompliance in 28 (8/11/9), and other reasons in 17 (9/5/3) patients. There were 24 (14/10) protocol violations, which included a TSS <4 points at baseline in 11 (6/5), breaking of the code in 3 (2/1), duration of intravenous treatment exceeding 28 days in 5 (3/2), and other reasons in 5 (3/2) patients.

The rates of adverse events during the intravenous treatment period were 72/341 (21.1%) in the group given α-lipoic acid and 41/168 (24.4%) in the placebo group. During the oral treatment phase, the rates of adverse reactions were 77/167 (46.1%) in A-A, 66/174 (37.9%) in A-P, and 75/168 (44.6%) in P-P, without significant differences between the groups.

Analysis

The mean HbA_{1c} levels decreased from baseline to day 19 from 8.5 ± 0.2% to 8.3 ± 0.2% and 8.2 ± 0.2% after the oral treatment period in A-A, from 8.7 ± 0.1% to 8.5 ± 0.2% and 8.5 ± 0.2% in A-P, and from 8.7 ± 0.1% to 8.3 ± 0.1% and 8.4 ± 0.2% in P-P. No significant differences were noted for the mean changes in HbA_{1c} during the study between the three groups examined.

The median changes in the TSS in the foot, NIS, and NIS(LL) from baseline to day 19 and the AUC for the TSS during the intravenous treatment period in the groups treated with α-lipoic acid and placebo are shown in Table 2. The decrement in the TSS was more pronounced by 19% in the group treated with α-lipoic acid than in the placebo group, but this difference did not reach statistical significance. The AUC was significantly smaller in the active as compared with the placebo group ($P = 0.033$). After 19 days, the NIS decreased significantly in the patients treated with α-lipoic acid as compared with those given placebo ($P = 0.016$), while the corresponding decrease in the NIS(LL) achieved borderline significance ($P = 0.055$).

The changes in the TSS, NIS, and NIS(LL) after completion of the oral treatment phase are shown in Table 3. The median decrease in the TSS from baseline was identical in the three groups studied. Analysis of the intercenter variability in the TSS revealed an increase in the CV from 13.7% (2.4–38.2%) at baseline to 26.1% (2.4.–65.9%) after day 19 and to 29.3% (7.9–82.0%) after 6 months of oral treatment in A-A, from 9.8% (3.7–28.7%) to 24.4% (7.1–43.0%) and 37.0% (8.3–58.5%) in A-P, and from 11.7% (3.1–30.3%) to 27.7% (5.1–61.8%) and 22.0% (3.5–79.3%) in P-P, indicating that the quality of data generated with the TSS may have decreased during the study.

After completion of the oral treatment period, there was a trend of borderline significance toward a reduction in both the NIS and NIS(LL) only in the A-A group as compared with the P-P group (both $P = 0.09$) (Table 3). The CVs for intercenter variability in the NIS were 23.3% (3.8–40.6%) at baseline, 26.5% (7.9–100%) after 19 days, and 25.3% (9.1–100%) after 6 months of oral treatment in A-A. The corresponding CVs for A-P were 17.2% (5.9–44.3%), 23.9% (7.3–100%), and 26.6% (0–100%) and those for P-P were 22.2% (7.1–49.9%), 29.3% (7.7–66.1%), and 27.3% (4.4–78.5%), indicating a relatively constant quality of data generation.

Table 2—*Changes in the TSS, NIS, and NIS(LL) after 19 days of intravenous treatment versus baseline and AUC for TSS*

	α-Lipoic acid	*n*	Placebo	*n*	*P* value
TSS (Day 19 vs. 1)	−3.7 (−12.6 to 5.0)	338	−3.0 (−12.3 to 8.0)	165	0.447
TSS (AUC)	85.6 (0 to 219)	338	95.9 (5.5 to 220)	165	0.033
NIS (Day 19 vs. 1)	−4.34 ± 0.35	314	−3.49 ± 0.58	154	0.016
NIS(LL) (Day 19 vs. 1)	−3.32 ± 0.26	314	−2.79 ± 0.42	154	0.055

Data are medians (range), *n*, or means ± SEM.

CONCLUSIONS — The ALADIN III Study could not demonstrate an a priori specified effect on the TSS as the primary outcome measure of the overall neuropathic symptom severity and frequency after 19 days and 7 months of treatment with α-lipoic acid in type 2 diabetic outpatients with polyneuropathy. This was possibly due to increasing intercenter variability in symptom scoring during the study and other factors. However, exploratory analysis showed that parenteral treatment with 600 mg α-lipoic acid over 3 weeks was associated with a significant reduction of neuropathic deficits as assessed by the NIS. After subsequent 6-month oral treatment with 600 mg α-lipoic acid three times a day, a trend of borderline significance toward such an improvement was found as compared with placebo treatment. These data raise doubt regarding the use of neuropathic symptoms as the primary criterion of efficacy in designs of future clinical trials of diabetic neuropathy. Both parenteral and oral treatments were safe over the period studied.

In a previous dose-finding trial (ALADIN Study), we have shown that intravenous treatment with α-lipoic acid using a dose of 600 mg/day for 3 weeks ameliorates the TSS and that a dose of 1,200 mg/day for 3 weeks improves the Neuropathy Disability Score (NDS) in type 2 diabetic patients with polyneuropathy (24). Regarding oral treatment with α-lipoic acid, in the DEKAN Study we recently demonstrated an improvement in HRV after 4 months using 800 mg/day in type 2 diabetic patients with cardiac autonomic neuropathy (25). The results of the ALADIN III Study appear to resemble some, but not all, of the findings of the ALADIN and DEKAN studies, and it extends the current evidence of the longer-term effects of α-lipoic acid. First, the beneficial effect of 3-week intravenous treatment with 1,200 mg on the NDS in the ALADIN Study is compatible with the improvement of the NIS with 600 mg seen in the present study. The mechanisms of such rapid improvement are unknown, but they may be related to improvement in nerve blood flow mediated by the antioxidant action of the drug (9,13). The reasons for the lacking effect of 600 mg in the ALADIN Study (24) could have been the smaller number of patients included in that study and the use of the NDS suggested by Young et al. (28), which has been developed for epidemiological purposes rather than controlled clinical trials and represents a simplified approach to quantify neuropathic deficits when compared with the NIS proposed by Dyck et al. (27). Thus, the NIS, as used in the present study, appears to be more suitable to detect changes in neuropathic deficits induced by an intervention.

Second, the trend of borderline significance toward improvement in the NIS and NIS(LL) after 6 months of oral treatment

Table 3—*Changes in the TSS, NIS, and the NIS(LL) after 7 months versus baseline in the three groups studied*

	A-A	*n*	A-P	*n*	P-P	*n*
TSS	−3.98 (−12.64 to 5.66)	165	−3.99 (−12.31 to 5.33)	173	−3.98 (−12.32 to 8.32)	165
NIS	−5.82 ± 0.73*	119	−5.76 ± 0.69	121	−4.37 ± 0.83	124
NIS(LL)	−4.39 ± 0.51*	120	−4.20 ± 0.52	123	−3.37 ± 0.54	125

Data are medians (range), *n*, or means ± SEM. *$P = 0.09$ vs. P-P.

points in the same direction as does the improvement in HRV after 4 months seen in the DEKAN Study: This suggests that oral treatment with α-lipoic acid over several months may favorably influence the principal measures of neuropathic impairment. It has recently been suggested by the Peripheral Nerve Society that the most convincing evidence that a pharmaceutical agent is efficacious is if it prevents, stabilizes, or improves global neuropathic deficit (impairment) (29). Furthermore, neuropathic deficits such as impaired vibration perception threshold predict the development of neuropathic foot ulcers (30) and possibly increased mortality (3). Hence, any treatment that could beneficially influence such deficits would be valuable.

Third, in contrast to the ALADIN Study, the primary criterion of efficacy was not met in the present study, i.e., the change in the TSS was not significantly different in favor of the group receiving α-lipoic acid after 3 weeks of intravenous treatment. However, the AUC computed post-hoc from the TSS on a daily basis was significantly lower in the group given α-lipoic acid, suggesting a favorable, albeit small, effect throughout the intravenous treatment period. Several reasons for the apparently divergent result between the ALADIN and ALADIN III studies regarding the TSS are conceivable: *1*) the different entry criteria of the two studies; *2*) the higher placebo response in ALADIN III than in ALADIN (46.7 vs. 38.4%); *3*) the relatively high number of participating centers, the majority of which included only a few patients; *4*) the fact that, in contrast to the NIS, which was assessed by the physicians, the TSS was allowed to be carried out by the study nurses, who may have differed within one center; this obviously contributed to the increasing degree of intercenter variability in the TSS, indicating a decreasing quality of data generation for the TSS in contrast to the NIS during the trial; *5*) the fact that the estimated number of n = 582 patients needed to detect a prespecified treatment difference of 1.0 in the TSS between the α-lipoic acid and placebo groups after 19 days and a standard deviation of s = 3.5 could not be completed, since recruitment had to be terminated prematurely because of technical reasons; and *6*) the relatively high dropout rate of 25% during the trial. We believe that the apparently divergent result for the TSS compared with the NIS in this study is largely explicable on the basis of these arguments. Moreover, there is now general agreement that assessment of deficits rather than symptoms alone should be included as a primary criterion of efficacy in future controlled clinical trials of diabetic neuropathy (29).

The apparent decrease in the NIS during this study in the placebo-treated patients deserves comment. One reason could be the therapeutic expectations of both the patients and physicians, who may perform better when they expect improvement. Since this was a randomized controlled trial, only an improvement exceeding the placebo response is of relevance. Hence, the magnitude of the mean difference in the NIS of 1.5 points between the active and placebo groups after 6 months of oral treatment is of interest. The Peripheral Nerve Society suggested that a mean change of 2 NIS points is sufficiently large to be considered a clinically meaningful effect of an intervention on diabetic polyneuropathy (29). From power estimates based on the Rochester Diabetic Neuropathy Study cohort, assuming that a treatment may prevent worsening of the neuropathy, controlled clinical trials would need to be conducted for a period of 3 years with 70 persons in each arm to achieve a difference of ≥2 NIS points (27). In a recent 6-month trial of recombinant human nerve growth factor, there was only a nonsignificant mean difference of 0.4 or 0.8 points in the NIS(LL) between the 0.1 or 0.3 μg/kg dose groups and placebo, respectively, despite concomitant improvement in multiple end-point analyses (14). Hence, we feel that the mean difference of 1.5 NIS points found in the present study approaches clinical significance within 7 months of treatment with α-lipoic acid. The reasons for the statistically borderline significance for the NIS after 7 months compared with the $P < 0.05$ level at 19 days may be that three groups were tested after the oral period but two after the intravenous phase and that an increasing number of dropouts has been included in the intention-to-treat analysis after the oral treatment period. It is tempting to speculate that prolonged treatment over several years could yield a definitely clinically meaningful effect on the NIS.

Evidence has accumulated indicating that the initial diabetes-related changes in the nerve are mediated by oxidative stress, which, on a long-term basis, could result in progressive neuronal damage. Thus, a potential is given for treating diabetic neuropathy using antioxidants such as α-lipoic acid as a pathogenetically oriented treatment approach. For the reasons outlined above, the ALADIN III Study could not demonstrate an a priori specified effect on neuropathic symptoms, but it indicates some clinically meaningful effects on neuropathic deficits after 19 days and 7 months of treatment with α-lipoic acid. The present results challenge the use of neuropathic symptoms as the primary criterion of efficacy in future clinical trials of diabetic neuropathy. This has been considered in the design of a pivotal 4-year multicenter trial of oral treatment with α-lipoic acid (Neurological Assessment of Thioctic Acid in Neuropathy Study) aimed at slowing the progression of diabetic polyneuropathy using a clinically meaningful and reliable primary end point that combines assessment of neuropathic deficits and neurophysiological measures.

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APPENDIX

Participants in the ALADIN III Study

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