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Treatment of symptomatic diabetic peripheral neuropathy with the anti-oxidant α-lipoic acid

A 3-week multicentre randomized controlled trial (ALADIN Study)

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Summary Anti-oxidant treatment has been shown to prevent nerve dysfunction in experimental diabetes mellitus, thus providing a rationale of potential therapeutic value for diabetic patients. The effects of the anti-oxidant α-lipoic acid (thioctic acid) were studied in a 3-week multicentre, randomized, double-blind placebo-controlled trial (**A**lpha-**L**ipoic **A**cid in **Di**abetic **N**europathy; ALADIN) in 328 non-insulin-dependent diabetic patients with symptomatic peripheral neuropathy who were randomly assigned to treatment with intravenous infusion of α-lipoic acid using three doses (1200, 600, or 100 mg ALA) or placebo (PLAC). Neuropathic symptoms (pain, burning, paraesthesiae, and numbness) were scored at baseline and at each visit (days 2–5, 8–12, and 15–19) prior to infusion. In addition, the Hamburg Pain Adjective List, a multidimensional specific pain questionnaire, and the Neuropathy Symptom and Disability Scores were assessed at baseline and day 19. According to the protocol 260 (65/63/66/66) patients completed the study. The total symptom score in the feet decreased from baseline to day 19 by -4.5 ± 3.7 ($-58.6\,\%$) points (mean ± SD) in ALA 1200, -5.0 ± 4.1 ($-63.5\,\%$) points in ALA 600, -3.3 ± 2.8 ($-43.2\,\%$) points in ALA 100, and -2.6 ± 3.2 ($-38.4\,\%$) points in PLAC (ALA 1200 vs PLAC: $p = 0.003$; ALA 600 vs PLAC: $p < 0.001$). The response rates after 19 days, defined as an improvement in the total symptom score of at least 30 %, were 70.8 % in ALA 1200, 82.5 % in ALA 600, 65.2 % in ALA 100, and 57.6 % in PLAC (ALA 600 vs PLAC; $p = 0.002$). The total scale of the Pain Adjective List was significantly reduced in ALA 1200 and ALA 600 as compared with PLAC after 19 days (both $p < 0.01$). The rates of adverse events were 32.6 % in ALA 1200, 18.2 % in ALA 600, 13.6 % in ALA 100, and 20.7 % in PLAC. These findings substantiate that intravenous treatment with α-lipoic acid using a dose of 600 mg/day over 3 weeks is superior to placebo in reducing symptoms of diabetic peripheral neuropathy, without causing significant adverse reactions. [Diabetologia (1995) 38: 1425–1433]

Key words Diabetic neuropathy, symptom scores, treatment, anti-oxidants, α-lipoic acid.

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* A list of the participants in the ALADIN Study appears in the acknowledgements

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Abbreviations: ALA, α-lipoic acid; HPAL, Hamburg Pain Adjective List; NCV, nerve conduction velocity; NDS, Neuropathy Disability Score; NSS, Neuropathy Symptom Score; TSS, total symptom score; VPT, vibration perception threshold; NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus.

Near-normoglycaemia is now generally accepted as the primary goal in prevention of diabetic neuropathy [1, 2]. However, in diabetic patients with advanced stages of peripheral neuropathy relatively long periods of near normal glycaemic control for several months or even years may be needed to retard the progression of nerve dysfunction [3, 4]. Hence, in symptomatic diabetic neuropathy additional pharmacological treatment of painful neuropathic symptoms is frequently required to maintain quality of life. Although treatment of pain with tricyclic antidepressants such as amitriptyline is effective [5, 6], it

may be of limited value due to frequent adverse reactions [5] or increased risk of mortality from overdose [7]. Other symptomatic approaches including anticonvulsants [6], mexiletine [8], and topical capsaicin [9] have either not been unequivocally effective [6], have shown only partial effects [8], or caution has been urged as to potential neurotoxic side effects in view of longer-term treatment [10]. Furthermore, these medications are only designed to modulate symptoms without influencing the underlying neuropathy.

Potential forms of treatment that have emerged from the current concepts on the pathogenesis of diabetic neuropathy include the reduction of increased flux through the polyol pathway using aldose reductase inhibitors [11, 12], substitution of *myo*-inositol [13], inhibition of the formation of advanced glycation end products by aminoguanidine [14], correction of depleted neurotrophic factors by nerve growth factor substitution [15], elimination by vasodilators of endoneurial hypoperfusion resulting in hypoxia [16], correction of alterations in essential fatty acid metabolism by gamma-linolenic acid [17], and substitution of acetyl-L-carnitine [18]. Although some of these experimental therapeutic approaches have been investigated in human diabetic neuropathy, their efficacy has not yet been unequivocally established and in any case, these medications are not available in most countries.

There is accumulating evidence suggesting that free-radical-mediated oxidative stress is implicated in the pathogenesis of diabetic neuropathy by inducing neurovascular defects that result in endoneurial hypoxia and subsequent nerve dysfunction [19–21]. Administration of physiological anti-oxidants including α-lipoic acid, a potent lipophilic free radical scavenger [22], resulted in prevention of neurovascular abnormalities associated with experimental diabetic neuropathy [23–27], providing a basis of potential therapeutic value in diabetic patients. In fact, lipid-soluble anti-oxidants have recently been singled out as potential candidates for clinical studies [21].

In a randomized single-blind pilot study we have previously demonstrated an improvement in symptoms of diabetic neuropathy during a 3-week period of intravenous treatment with 600 mg of α-lipoic acid per day as compared with vitamin B_1 [28]. This finding in conjunction with recent experimental evidence [27] formed the rationale for a large-scale, multicentre, double-blind placebo-controlled trial designed to assess the efficacy and safety of three different doses of α-lipoic acid in non-insulin-dependent (NIDDM) diabetic out-patients with symptomatic peripheral neuropathy.

Subjects and methods

Study design. The **A**lpha-**L**ipoic **A**cid in **Di**abetic **N**europathy Study (ALADIN) was a randomized, double-blind placebo-controlled trial using three doses of the trometamol salt solution of α-lipoic acid (Thioctacid T, ASTA Medica, Frankfurt am Main, Germany) in four parallel treatment groups of NIDDM patients with symptomatic peripheral neuropathy. Intravenous infusion of 1200 mg (ALA 1200), 600 mg (ALA 600), 100 mg (ALA 100) α-lipoic acid, or placebo in 250 ml 0.9 % isotonic saline solution over 30 min was administered once daily over two 5-day periods (Monday to Friday) and one 4-day period (Monday to Thursday) during 3 consecutive weeks. Ampules containing 10 ml (250 mg) and 4 ml (100 mg) α-lipoic acid or placebo were used. Each patient received six ampules containing 48 ml in total (four ampules with 10 ml each and two ampules with 4 ml each): ALA 1200: 40 ml (1000 mg) and 8 ml (200 mg); ALA 600: 20 ml (500 mg), 4 ml (100 mg), and 24 ml placebo; ALA 100: 4 ml (100 mg) and 44 ml placebo; placebo: 48 ml placebo. Because of the yellow colour of the α-lipoic acid containing solutions, riboflavin (0.00375 mg/ml) was added to the placebo to obtain a preparation of the same colour. Thus, the colour of the solutions containing the three doses of α-lipoic acid and placebo was identical.

The study was designed as a confirmatory comparison of the group treated with 600 mg α-lipoic acid with placebo after 19 days using a total symptom score as the primary endpoint.

Subjects. After approval by the ethical committee of the Landesärztekammer, Brandenburg, Germany, and written informed consent had been obtained, 328 patients were recruited from 38 out-patient centres in Germany. They were randomly assigned to receive one of four treatments: α-lipoic acid 1200 mg (ALA 1200), 600 mg (ALA 600), 100 mg (ALA 100), or placebo according to their entry sequence following a central computerized randomization list. All investigators and patients were "blinded" to the randomization of the study drug assignments.

Patients were eligible if they were aged 18 years and over and less than 70 years, had NIDDM treated with diet, oral anti-diabetic agents and/or insulin, and had evidence of symptomatic symmetrical distal neuropathy (reduced/absent ankle reflexes, reduced vibration, thermal, tactile, pin-prick, and/or position sensation) with at least moderate severity of one or more of the typical symptoms (burning, paraesthesiae, numbness) in the feet equivalent to 2 or more points in the total symptom score (outlined in Methods). Exclusion criteria were: 1) severe neuropathy including paresis, muscle atrophy, and very severe sensory deficits with reduced vibration or thermal sensation at five or six testing sites, respectively; 2) peripheral vascular disease (non-palpable foot pulses, intermittent claudication); 3) causes of neuropathy other than diabetes (e.g. chronic alcohol abuse, drug-induced neuropathy), truncal neuropathy, and significant neurological diseases (e.g. Parkinson's disease, epilepsy, multiple sclerosis); 4) use of medication likely to interfere with the interpretation of the results (e.g. antidepressants, anticonvulsants, opiates, mexiletine, capsaicin, neuroleptics, vitamin B compounds, gamma-linolenic acid, aldose reductase inhibitors, anti-oxidants; 5) participation in another study; 6) severe concomitant diseases (e.g. malignancies, hepatic or renal disease); 7) pregnancy, lactation, or childbearing age without safe contraception.

The baseline clinical characteristics of the four groups studied according to the protocol 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.

Table 1. Clinical characteristics of the patients at entry into the study

	α-Lipoic acid 1200 mg	α-Lipoic acid 600 mg	α-Lipoic acid 100 mg	Placebo
Number	65	63	66	66
Sex (male/female)	40/60	37/63	51/49	35/65
Age (years)	59.2 ± 7.7	57.5 ± 8.7	58.7 ± 7.9	60.2 ± 7.7
Body mass index (kg/m^2)	29.2 ± 4.8	27.7 ± 4.9	27.8 ± 4.4	29.7 ± 4.9
Systolic blood pressure (mm Hg)	144 ± 16	143 ± 16	145 ± 15	144 ± 14
Diastolic blood pressure (mm Hg)	85 ± 9	85 ± 6	84 ± 8	84 ± 9
Smokers[a]	11	13	14	14
Duration of diabetes (years)	11.0 ± 7.3	10.4 ± 7.1	11.7 ± 7.0	12.3 ± 7.7
Insulin treatment[a]	57	67	68	65
Blood glucose (mmol/l)	11.1 ± 4.1	11.2 ± 4.1	11.4 ± 4.3	11.0 ± 3.6
HbA_1 (%)	8.8 ± 1.9	9.2 ± 2.5	9.0 ± 2.1	9.4 ± 2.6
Retinopathy[a]	34	30	27	38
Duration of neuropathy (years)	3.3 ± 4.1	2.8 ± 2.6	2.8 ± 2.6	3.4 ± 3.7
Symptom score: Pain	2.02 ± 1.18	2.08 ± 1.15	1.82 ± 1.24	1.70 ± 1.24
Burning	1.51 ± 1.32	1.63 ± 1.29	1.77 ± 1.32	1.24 ± 1.31
Paraesthesiae	2.06 ± 1.08	1.93 ± 1.23	2.04 ± 1.30	1.98 ± 1.12
Numbness	2.04 ± 1.24	2.17 ± 1.28	1.95 ± 1.34	1.89 ± 1.32
Neuropathy Symptom Score	5.3 ± 1.8	5.6 ± 2.0	5.0 ± 1.9	5.3 ± 1.7
Neuropathy Disability Score	6.1 ± 2.7	6.0 ± 2.5	6.2 ± 2.6	6.2 ± 2.4
Pain Adjective List (total scale)	2.01 ± 1.44	2.14 ± 1.51	2.17 ± 1.40	2.06 ± 1.41

Values are mean ± SD or [a] percentage of patients

Table 2. Scoring approach for the neuropathic symptoms included in the total symptom score (pain, burning, paraesthesiae, numbness)

Symptom frequency	Symptom intensity			
	Absent	Slight	Moderate	Severe
Occasional	0	1.00	2.00	3.00
Frequent	0	1.33	2.33	3.33
(Almost) continuous	0	1.66	2.66	3.66

Efficacy assessments

Primary outcome measure. At baseline (day 1) and each subsequent visit (days 2–5, 8–12, and 15–19) prior to infusion, neuropathic symptoms (pain, burning, paraesthesiae and numbness) were scored for severity by the physician or a trained nurse. We have chosen an approach similar to a graphic rating scale [29] that uses descriptive terms to assist the patient in deciding the position of his/her score. Our approach takes into account both the intensity and frequency of each of the four symptoms in equidistant steps (Table 2). A total symptom score (TSS) ranging from 0 (no symptoms) to a maximum of 14.64 points (all symptoms are severe and [almost] continuously present) was used as a primary outcome measure. An improvement in the TSS of at least 30% (or ≥ 2 points in patients with ≤ 4 points at entry) from baseline to day 19 was defined as a clinically meaningful response to treatment.

Secondary outcome measures. The Neuropathy Symptom Score (NSS) was completed according to Young et al. [30] at baseline and each visit, and the Neuropathy Disability Score (NDS) [30] was assessed at baseline and on day 19 by the physician who also completed a global judgement of efficacy and tolerability of the drug (very good/good, satisfactory, inadequate, not ratable) on that day. Instruments used in the assessment of the NDS included a 128-Hz tuning fork for measurement of the vibration perception threshold (VPT) on the foot (great toe, sole, dorsum, medial malleolus, mid and head of tibia) and a Thermit device (Axon, Düsseldorf, Germany) for examination of thermal sensation (identical sites, sole excepted). Abnormal VPT was defined as values less than 4/8 and abnormal thermal sensation as a lack of temperature discrimination between the two plates of the device.

The Hamburg Pain Adjective List (HPAL), a multidimensional specific pain questionnaire devised by Hoppe [31], was filled in by the patient at baseline and on day 19. The HPAL includes 37 adjectives to describe pain "as it is usually". These adjectives have to be rated in seven steps ranging from "absolutely incorrect" (0 points) to "absolutely correct" (6 points). The items are summarized to four primary scales and three additional scales, respectively. Primary scales describe: 1) pain suffering by 12 items; 2) fear of pain by 9 items; 3) pain acuity by 9 items; 4) pain rhythm by 7 items. Pain suffering and fear of pain represent the affective component (21 items), while pain acuity and pain rhythm represent the sensory component (16 items). Affective and sensory components constitute additional scales. The third additional scale is the total scale (37 items) which provides a measure of the general pain intensity. In the analysis of the HPAL the resulting points were added separately for each scale. Increasing values indicate an increasing intensity of the individual pain component. The time needed by the patient to answer all items of the HPAL was 5–10 min.

Laboratory methods. Glycated haemoglobin (HbA_{1a-c}) was determined at baseline and on day 19 with the HPLC technique using a Diamat analysing system (Bio-Rad, Munich, Germany). The normal range being < 7.7% of total haemoglobin. Capillary blood glucose was taken at baseline and at each visit (days 2–5, 8–12, and 15–19) prior to the infusion and thereafter using heparinized capillary blood (20 µl) and was measured by the hexokinase method on an ACP 5040 autoanalyser (Eppendorf, Hamburg, Germany).

Safety parameters were determined at baseline and on day 19 (liver enzymes, creatinine, haemoglobin, full blood count, total protein, bilirubin, uric acid, cholesterol, and triglycerides).

Statistical analysis

The continuous data listed in Table 1 are expressed by the arithmetic mean ± SD. The efficacy of the randomization process in balancing the groups with regard to the variables presented in Table 1 was analysed using Fisher's exact test for categorical data and ANOVA for continuous data. *P*-values less than 0.1 were considered to be a sign of inhomogeneity. The follow-up data are given as the arithmetic mean ± SEM. Differences between groups were analysed using the *t*-test for two independent samples. The paired *t*-test was employed to test differences over time. The changes in the TSS from baseline to the follow-up visits are given on a daily basis as the arithmetic mean ± SEM (negative values in the text signify improvement). These changes were tested between the groups on days 5, 12, and 19 using the *t*-test for two independent samples. Qualitative data are given as relative frequencies which were analysed by the Fisher's exact test.

The comparison of ALA 600 with placebo regarding the response rates (improvement in the TSS by at least 30 % or ≥ 2 points in patients with ≤ 4 points at entry) after 19 days was defined as the primary confirmatory criterion of efficacy. In addition, the time to response (i.e. onset of efficacy), as assessed by the symptom scores (burning, paraesthesiae, numbness) in the foot, was used exploratively as an alternative response criterion. Focussing on intensity only, the time to response was defined as an improvement in one of these scores by at least 1 point as compared with baseline. The time to response analysis was based on the assumption that once the response to a particular symptom occurs, the latter cannot deteriorate later. The time to response data were analysed using the Kaplan–Meier (Product Limit) estimators, and the distribution curves were compared between the groups using the log-rank (Mantel–Haenszel) test. The level of significance for invariably two-tailed testing was set uniformly at $\alpha = 0.05$, and comparisons of the treatment groups were based on a per-protocol analysis in order to ascertain efficacy in patients who adhered to the protocol and the assigned treatment [32]. Only comparisons between the placebo group and each of the groups receiving α-lipoic acid were performed.

A comparison of the time to response in one score between ALA 600 and placebo was defined as the primary criterion with which to estimate the sample size required to detect an a priori specific treatment difference. Assuming that the placebo response rate approximates 30 % and that of ALA 600 yields 60 % after 19 days and calculating a drop-out rate of 30 %, the required number of patients is estimated at $n = 67$ per group, with $\alpha = 0.05$ and $\beta = 0.1$ for the two-tailed log-rank test.

Results

Analysis of withdrawals and safety monitoring. Among the 328 patients recruited, 326 were entered into the study (ALA 1200: $n = 86$/ALA 600: $n = 77$/ ALA 100: $n = 81$/placebo: $n = 82$), while 2 patients were not available after recruitment. Among 15 withdrawals during the study, 8 (5/1/1/1) patients dropped out due to drug intolerance including mainly adverse gastrointestinal events, 2 (0/0/1/1) patients due to intercurrent disease, 3 (3/0/0/0) patients due to non-compliance, and 2 (0/0/2/0) patients for other reasons. A further 51 (13/13/11/14) patients were excluded from analysis, because they did not meet the inclusion and/or exclusion criteria. These protocol violations included age over 70 years ($n = 10$), very severe sensory deficits with reduced vibration or thermal sensation at five or six testing sites ($n = 3$), use of drugs likely to interfere with the results of the study ($n = 5$), severity less than 2 points in the TSS of one or more of the symptoms in the feet ($n = 29$), and inappropriate administration of study medication ($n = 4$). Thus, according to the protocol 260 (65/63/ 66/66) patients were included in the analysis.

The rates of adverse events were 28 of 86 (32.6 %) in ALA 1200, 14 of 77 (18.2 %) in ALA 600, 11 of 81 (13.6 %) in ALA 100, and 17 of 82 (20.7 %) in placebo. Adverse events that occurred in 5 or more patients per group included headache (5/6/6/8) and gastrointestinal reactions which were almost restricted to ALA 1200: nausea (13/2/1/1) and vomiting (8/0/0/ 0) ($p < 0.05$) for ALA 1200 vs the remaining groups).

Glycaemic control. The mean HbA_1 levels decreased from baseline to day 19 from 8.8 ± 0.3 to 8.6 ± 0.3 % in ALA 1200, from 9.0 ± 0.4 to 8.6 ± 0.3 % in ALA 600, from 9.0 ± 0.3 to 8.6 ± 0.3 % in ALA 100, and from 9.4 ± 0.4 to 9.0 ± 0.3 % in placebo. No significant differences were noted for the mean changes in HbA_1 between the four groups studied. The blood glucose levels measured prior to the infusion on days 2–5, 8–12, and 15–18 were significantly lower than at baseline on 4 days in ALA 1200, 1 day in ALA 600, 1 day in ALA 100, and on 3 days in placebo. The mean pre-infusion blood glucose levels on days 2–18 were 10.3 ± 0.4 mmol/l in ALA 1200, 10.8 ± 0.4 mmol/l in ALA 600, 11.1 ± 0.5 mmol/l in ALA 100, and 10.4 ± 0.3 mmol/l in placebo, without significant differences between the groups.

Symptom scores. The mean changes in the TSS as compared with baseline on a daily basis in the four groups studied are shown in Figure 1. There was a significant decrease from baseline which was first observed on days 2 or 3 in each of the four groups studied (all $p < 0.05$). The decrease in TSS over baseline was significantly more pronounced after 5 days in ALA 1200, ALA 600, and ALA 100 than in placebo (all $p < 0.01$) and after 12 and 19 days in ALA 1200 and ALA 600 than in placebo (all $p < 0.01$).

The mean changes in the individual scores for burning, paraesthesiae, numbness, and pain from baseline to day 19 are illustrated in Figure 2. The reduction after 19 days was significantly higher for burning, paraesthesiae, and numbness in ALA 1200 and ALA 600 than in placebo (all $p < 0.05$), and for pain

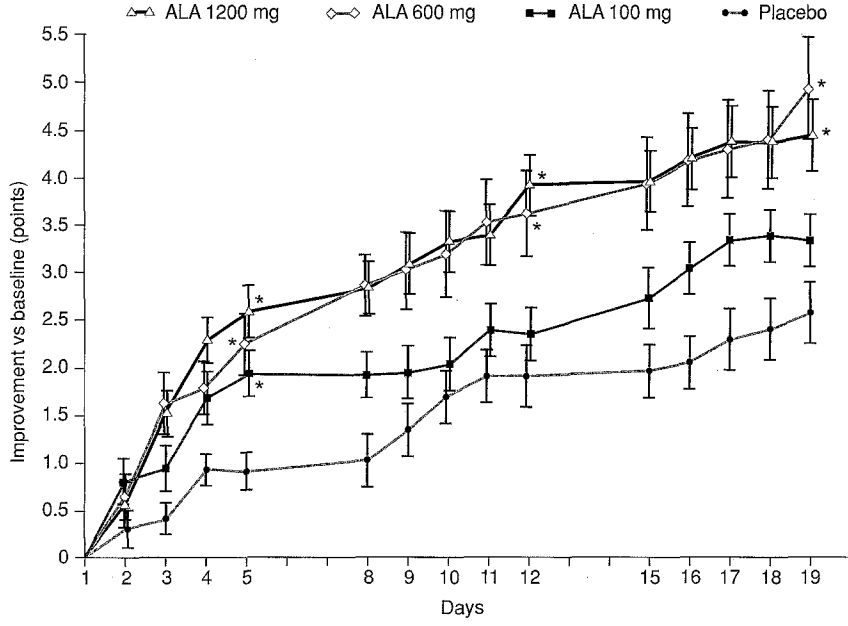

Fig. 1. Changes (improvement) in the total symptom scores (TSS) from baseline on a daily basis in the four groups studied (mean ± SEM). * $p < 0.05$ vs changes in placebo for statistical testing after 5, 12, and 18 days

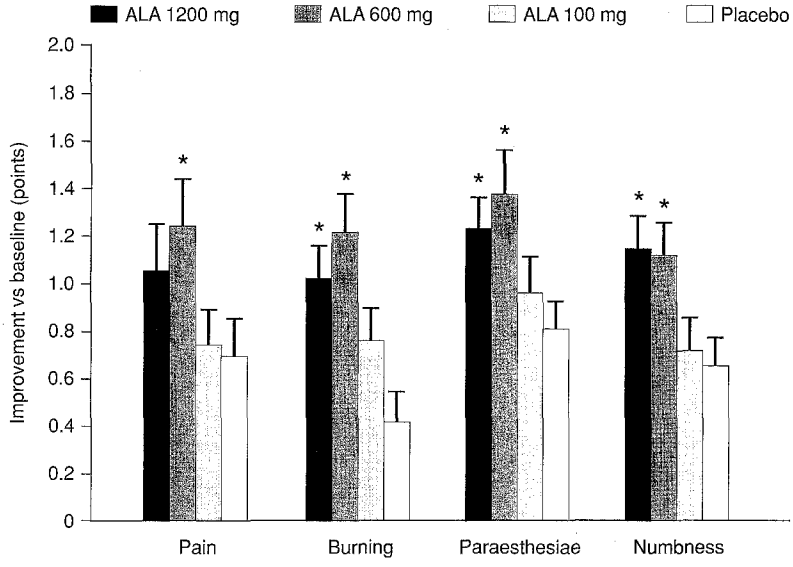

Fig. 2. Changes (improvement) in the individual scores for burning, paraesthesiae, numbness, and pain from baseline to day 19 in the four groups studied (mean ± SEM). * $p < 0.05$ vs changes in placebo

in ALA 600 as compared with placebo ($p = 0.02$). There were no significant differences in the reduction of these symptoms between ALA 100 and placebo after 19 days. When additional statistical testing was performed on days 5 and 12, significant differences between ALA 1200 and placebo were noted on both days for all symptoms (all $p < 0.05$), between ALA 600 and placebo on both days for pain and burning ($p < 0.05$) and on day 5 for numbness ($p = 0.02$), and between ALA 100 and placebo on day 5 for pain and burning ($p < 0.05$) (data not shown).

The response rates after 19 days, defined as an improvement in the TSS in the foot of at least 30 % (or ≥ 2 points in patients with ≤ 4 points at entry) were 46 of 65 (70.8 %) in ALA 1200, 52 of 63 (82.5 %) in ALA 600, 43 of 66 (65.2 %) in ALA 100, and 38 of 66 (57.6 %) in placebo ($p = 0.002$ for ALA 600 vs placebo).

The time to response curves, defined as an improvement in one score (burning, paraesthesiae, or numbness) by at least 1 point (see statistical analysis), are presented in Figure 3. The rates of non-responders obtained by this definition were significantly lower after 19 days in ALA 1200 and ALA 600 as compared with placebo ($p < 0.05$), but no such difference was observed for ALA 100.

Multidimensional pain assessment. The mean changes from baseline to day 19 in the total scale of the Hamburg Pain Adjective List (HPAL) as a measure of the general pain intensity are shown in Figure 4. The reduction of pain intensity in the total scale was significantly greater in ALA 1200 and ALA 600 than in placebo (both $p < 0.01$), but not in ALA 100 as compared with placebo. Likewise, pain intensity in both the affective and sensory scales declined significantly

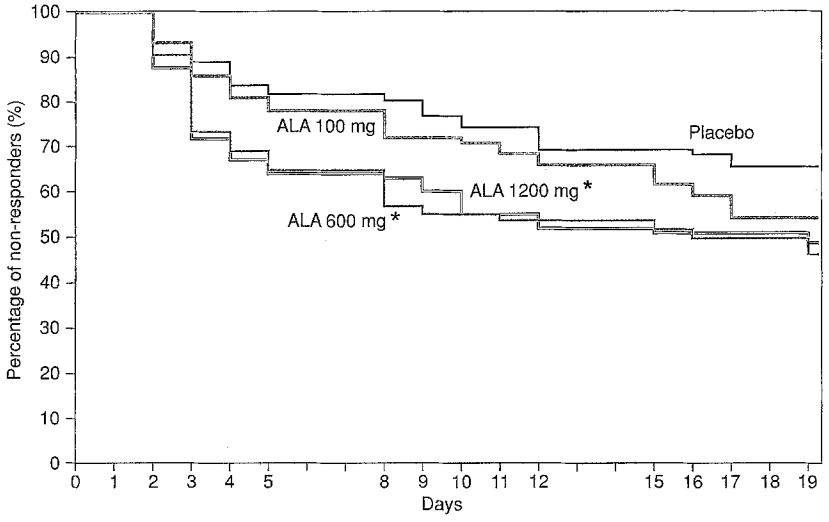

Fig. 3. Time to response curves, defined as an improvement in one score (burning, paraesthesiae, or numbness) by at least one point without deterioration during the remaining study period. The curves plotted illustrate the percentages of non-responders. * $p < 0.05$ vs placebo

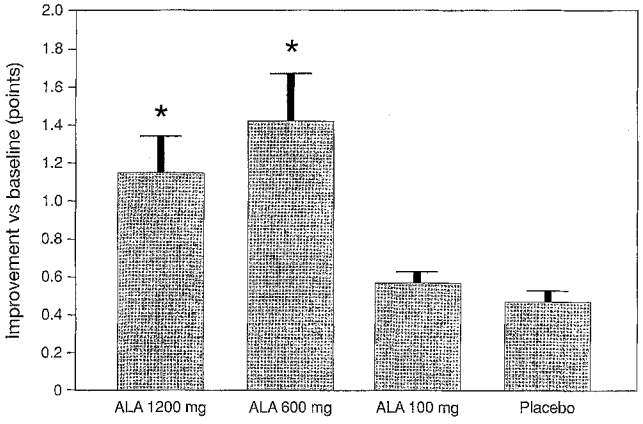

Fig. 4. Changes (improvement) from baseline to day 19 of the total scale of the Hamburg Pain Adjective List (HPAL) (mean ± SEM). * $p < 0.05$ vs changes in placebo

by − 1.4 ± 0.3 and − 0.8 ± 0.2 points in ALA 1200 and by − 1.6 ± 0.3 and − 1.1 ± 0.2 points in ALA 600 as compared with − 0.5 ± 0.1 and − 0.4 ± 0.1 points in placebo (all $p < 0.05$), but the reduction by − 0.6 ± 0.1 and − 0.6 ± 0.1 points in ALA 100 was similar to placebo.

Clinical signs. After 19 days the Neuropathy Disability Score (NDS) decreased by − 1.8 ± 0.3 points in ALA 1200, by − 1.5 ± 0.3 points in ALA 600, by − 0.9 ± 0.3 in ALA 100, and by − 1.0 ± 0.2 in placebo ($p = 0.03$ for ALA 1200 vs placebo).

Global rating. The percentages of patients rated as "very good/good efficacy" by the physician's global evaluation on day 19 were 40 of 65 (61.5 %) in ALA 1200, 48 of 63 (76.2 %) in ALA 600, 35 of 66 (53.0 %) in ALA 100, and 30 of 66 (45.5 %) in placebo ($p = 0.001$ for ALA 600 vs placebo). Overall drug tolerance rated as "very good/good" was 71 of 86 (82.6 %) in ALA 1200, 73 of 77 (94.8 %) in ALA 600, 75 of 81 (92.6 %) in ALA 100 and 80 of 82 (97.6 %) in placebo.

Discussion

The findings of the present study demonstrate that parenteral treatment with the anti-oxidant α-lipoic acid over 3 weeks using a dose of 600 mg per day in NIDDM patients is associated with a significant reduction of various symptoms of peripheral neuropathy including pain, paraesthesiae, and numbness as compared with placebo. Furthermore, we provide evidence that a dose of 100 mg per day does not exert an effect superior to that seen with placebo. Finally, an increase in the dosage to 1200 mg per day is associated with an enhanced rate of adverse events rather than with maximized efficacy, since the latter was comparable to that of 600 mg per day.

Previous double-blind controlled studies have not provided convincing data regarding the efficacy of α-lipoic acid in diabetic peripheral neuropathy. The only controlled study hitherto published in which α-lipoic acid was administered intravenously was conducted by Schulz et al. [33] who treated 31 insulin-dependent diabetic (IDDM) patients using 200 mg per day i. v. over 15 days. In that study no significant effect on neuropathic symptoms was noted, but the distal motor latencies in the median, peroneal, and tibial nerves improved significantly as compared with placebo treatment. In another controlled study over 12 weeks, Jörg et al. [34] treated 35 IDDM patients with clinical or electrophysiological signs of neuropathy with α-lipoic acid (600 mg/day orally) or a vitamin B combination (600 mg/day orally), respectively. No significant therapeutic effects were demonstrated for any of the parameters measured including sensory nerve conduction velocity (NCV), nerve action potentials to single and double stimuli, relative refractory period, and nerve ischaemia resistance. However, in that study neuropathic symptoms were not assessed. In a 3-week double-blind study, Sachse and Willms [35] used a relatively low oral dose of

300 mg per day in 10 diabetic patients. They could not detect any differences between drug and placebo treatment for subjective symptoms, NCV or vibration perception threshold (VPT).

However, these studies had several essential drawbacks which make it impossible to ascertain whether α-lipoic acid is an effective compound for treatment of diabetic polyneuropathy. First, in line with 95 % of the previously published randomized controlled clinical trials [36], did these studies not estimate the sample size required to detect an a priori specified treatment difference. In the present trial we reasoned from previous studies a placebo response of about 30 % and a drug response of about 60 %. The a priori estimate of the required sample size yielded $n = 67$ patients per group, with $\alpha = 0.05$ and $\beta = 0.1$ for the two-tailed log-rank test. Thus, it becomes evident that the groups treated in the aforementioned studies [33–35] were too small to detect differences in neuropathic symptoms. Second, in view of our results, the intravenous dose of α-lipoic acid chosen by Schulz et al. [33] was in fact too low to induce an effect. Third, the severity of the neuropathic symptoms was not scored and no detailed assessment of pain intensity was performed [33, 35]. For these reasons, the chiefly negative results of the previous controlled studies could be anticipated.

The results of this controlled trial confirm those of our previous single-blind pilot study [28] in that they provide evidence of an improvement in the major neuropathic symptoms after 3 weeks of intravenous treatment with 600 mg α-lipoic acid. This effect was noted not only for pain and paraesthesiae but also for burning and numbness, and when these symptoms were added to a total score, the difference compared to placebo was observed after only 5 days. During the following 2 weeks a continuously sustained improvement in this score was seen. Detailed analysis of pain using a multidimensional questionnaire revealed that both the affective and sensory components of pain, representing pain experience and pain perception, could be improved. Although administration of 1200 mg per day seemed to result in a slightly more pronounced effect than 600 mg per day on neuropathic symptoms after 5 days, particularly paraesthesiae, the response rates after 19 days tended to be higher with 600 mg per day. Moreover, the increased risk of gastrointestinal side effects associated with 1200 mg per day preclude this dose being used. On the other hand, the efficacy of 100 mg per day was not distinguishable from placebo for the majority of the parameters examined.

It is unlikely that the effects observed in this study were biased by an improvement in glycaemic control, since no significant differences between the groups treated with α-lipoic acid and placebo were noted for the changes in HbA_1 from baseline to day 19. Moreover, no significant differences between the groups were seen regarding the blood glucose levels during the study.

It may be argued that nerve conduction studies were not used as objective measures of neuropathy in this study. However, in a short-term study of this kind a significant difference between the groups treated with α-lipoic acid and the placebo group regarding NCV would not be likely to occur. Previous studies using drugs such as aldose reductase inhibitors have shown that NCV was either unchanged [37] or only minimally increased during several weeks of treatment [38]. The latter study [38] was subject to substantial criticism as to whether it showed a clinically meaningful degree of change or merely a physiological variation [39]. Moreover, a significant deterioration in NCV during placebo treatment usually does not occur even after 1 year [12]. By contrast, neuropathic symptoms have been shown to be susceptible to intervention within a few weeks. Painful symptoms, but not motor and sensory NCV, were improved after 4 weeks of treatment with sorbinil as compared with placebo [37], and withdrawal of tolrestat resulted in a rapid worsening of pain scores [40].

It may also be argued that the exclusion of 51 patients due to failure to adhere to the protocol potentially could have introduced bias. We chose a per-protocol analysis of those patients who fulfilled the criteria for entry into the study and adhered to the assigned treatment but were aware of the fact that this approach would exclude a certain number of patients from analysis. It has recently been emphasized that an intention-to-treat (as randomized) analysis of clinical trials has no advantage over a per-protocol analysis [32]. In fact, an additional analysis of the results of this study based on the intention-to-treat revealed no appreciable differences in the outcome of the parameters studied when compared with the per-protocol analysis, indicating that the adherence to the study protocol did not introduce bias.

The exact mechanisms by which α-lipoic acid exerts its effect on neuropathic symptoms have yet to be established, but at least two putative hypotheses should be discussed. First, α-lipoic acid may induce a dose-dependent sprouting of neurites in cultured neuroblastoma cells [41]. Changes in membrane fluidity that are mediated by the sulphohydryl groups of the substance are thought to be responsible for this effect. In the experimentally-induced acrylamide neuropathy there is a marked reduction of the sprouting phenomenon and distal neuropathy occurs due to the depletion of substances containing sulphohydryl groups, such as glutathione, in the axon [42]. Spontaneous sprouting and integrity of the membrane at the nerve terminal can be maintained by administration of α-lipoic acid in vivo and in vitro. Moreover, in animal experiments the compound promotes regeneration after partial denervation [42].

Such a protective effect of α-lipoic acid has also been demonstrated in hexacarbon-induced neuropathy [43].

The second, and presumably most relevant, mechanism of action is based on the property of α-lipoic acid to act as a radical scavenger. A growing body of evidence suggests that oxidative stress resulting from enhanced free-radical formation and/or defects in anti-oxidant defences is implicated in the development of various disorders [44] including neurodegenerative diseases [45]. Cellular injury induced by intracellular alterations in the metabolism of defence systems against oxidative stress may also be relevant in the pathogenesis of diabetic complications [46]. Increased free radical formation and changes in haemostatic variables related to endothelial damage have been found in NIDDM patients with microalbuminuria [47]. Furthermore, impaired cellular scavenging activity against oxidative stress has recently been demonstrated in NIDDM patients [48]. In experimental diabetic neuropathy, oxygen free radical activity in the sciatic nerve is increased [19, 20]. Anti-oxidant treatment with butylated hydroxytoluene [24], glutathione [23], probucol [25, 26], α-tocopherol [26], and α-lipoic acid [27] prevents both the evolution of motor and sensory nerve conduction deficits and abnormalities in nerve blood flow in experimental diabetes. Lipophilic free radical scavengers such as α-lipoic acid or probucol seem to be more effective than hydrophilic ones such as glutathione [21]. Conversely, treatment of non-diabetic rats with the pro-oxidant primaquine caused a reduction in nerve blood flow and NCV deficits [25]. Only recently, Nagamatsu et al. [27] have demonstrated a dose-dependent normalization in digital NCV, nerve blood flow and glutathione levels following treatment with α-lipoic acid in diabetic rats, suggesting that the improvement in neurovascular changes was induced by improving oxygen free radical scavenging activity. One mechanism of reduced nerve blood flow is the inhibitory effect of superoxide anion on nitric oxide synthase. Since nitric oxide synthase is reduced in experimental diabetic neuropathy [49], α-lipoic acid might prevent this inhibition by reducing oxidative stress [27].

It is conceivable 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 and therefore, would be of pathogenetic relevance. In the light of this, a potential basis is provided for treating diabetic neuropathy using anti-oxidants such as α-lipoic acid. Long-term studies of oral treatment with α-lipoic acid are needed to address the question as to whether the observed reduction in neuropathic symptoms is accompanied by long-term effects on objective neurophysiological parameters.

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