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Treatment of Diabetic Polyneuropathy with the Antioxidant Thioctic Acid (α-Lipoic Acid): A Two Year Multicenter Randomized Double-blind Placebo-controlled Trial (ALADIN II)

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Short-term trials with the antioxidant thioctic acid (TA) appear to improve neuropathic symptoms in diabetic patients, but the long-term response remains to be established. Therefore, Type 1 and Type 2 diabetic patients with symptomatic polyneuropathy were randomly assigned to three treatment regimens: (1) 2 × 600 mg of TA (TA 1200), (2) 600 mg of TA plus placebo (PLA) (TA 600) or (3) placebo and placebo (PLA). A trometamol salt solution of TA of 1200 or 600 mg or PLA was intravenously administered once daily for five consecutive days before enrolling the patients in the oral treatment phase. The study was prospective, PLA-controlled, randomized, double-blind and conducted for two years. Severity of diabetic neuropathy was assessed by the Neuropathy Disability Score (NDS) and electrophysiological attributes of the sural (sensory nerve conduction velocity (SNCV), sensory nerve action potential (SNAP)) and the tibial (motor nerve conduction velocity (MNCV), motor nerve distal latency (MNDL)) nerve. Statistical analysis was performed after independent reviewers excluded all patients with highly variable data allowing a final analysis of 65 patients (TA 1200: $n = 18$, TA 600: $n = 27$; PLA: $n = 20$). At baseline no significant differences were noted between the groups regarding the demographic variables and peripheral nerve function parameters for these 65 patients. Statistically significant changes after 24 months between TA and PLA were observed (mean ± SD) for sural SNCV: $+3.8 \pm 4.2$ m/s in TA 1200, $+3.0 \pm 3.0$ m/s in TA 600, -0.1 ± 4.8 m/s in PLA ($p < 0.05$ for TA 1200 and TA 600 vs. PLA); sural SNAP: $+0.6 \pm 2.5$ μV in TA 1200, $+0.3 \pm 1.4$ μV in TA 600, -0.7 ± 1.5 μV in PLA ($p = 0.076$ for TA 1200 vs. PLA and $p < 0.05$ for TA 600 vs. PLA), and in tibial MNCV: $+1.2 \pm 3.8$ m/s in TA 1200, -0.3 ± 5.2 m/s in TA 600, -1.5 ± 2.9 m/s in PLA ($p < 0.05$ for TA 1200 vs. PLA). No significant differences between the groups after 24 months were noted regarding the tibial MNDL and the NDS. We conclude that in a subgroup of patients after exclusion of patients with excessive test variability throughout the trial, TA appeared to have a beneficial effect on several attributes of nerve conduction.

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Keywords: Diabetic polyneuropathy, treatment, thioctic acid, α-lipoic acid, antioxidants

INTRODUCTION

The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) showed that near-normoglycemia prevents the development of diabetic complications including diabetic polyneuropathy.[1,2] Since only a limited number of diabetic patients are able to reach near normal blood glucose control, alternative therapeutic approaches are being evaluated to prevent or treat diabetic polyneuropathy. Various pharmaceutical compounds are being tested regarding their ability to favorably influence nerve dysfunction in experimental diabetes and diabetic patients.[3–12] These include the aldose reductase inhibitors, myo-inositol, γ-linolenic acid, aminoguanidine, nerve growth factor and vasodilators.[5–12] These therapeutic interventions have shown variable effects on peripheral nerve dysfunction but in general have not yet been accepted as standard treatment.

Recent experimental studies suggest that the imbalance of oxidative stress and antioxidant defense may play a role in the pathogenesis of diabetic polyneuropathy.[13–15] Thioctic acid (TA) has been shown to exert excellent antioxidant properties e.g. to recycle glutathione and in turn enhance Vitamin E and Vitamin C.[16–18] In experimental diabetic neuropathy TA increases endoneurial blood flow, reduces free radical mediated oxidative stress and raises the reduced glutathione content of the peripheral nerve in a dose-dependent fashion, thus leading to an improvement in peripheral nerve function.[19–21] Neuroregenerative effects of TA have also been observed in both neural cell culture and experimental diabetic polyneuropathy.[22–24] There is increasing evidence from recent short-term clinical studies that TA improves peripheral and autonomic nerve function in human diabetic polyneuropathy.[3,4,25] In the present trial we evaluated the efficacy and safety of 2-year treatment with TA on peripheral nerve function in patients with diabetic polyneuropathy.

METHODS

Study Design and Population

In this study (Alpha Lipoic Acid in Diabetic Neuropathy: ALADIN II) Type 1 and Type 2 diabetic patients with symptomatic diabetic polyneuropathy were randomly assigned to three treatment groups receiving six tablets per day. The study was prospective, double-blind and randomized. Patients in the first group (TA 1200) received six tablets containing 200 mg of TA (Thioctacid®, ASTA Medica AG Frankfurt am Main, Germany), the second (TA 600) three tablets containing 200 mg of TA and three tablets placebo (PLA) and the third (PLA) six tablets of PLA. A trometamol salt solution of TA (Thioctacid® T) of 1200 or 600 mg or PLA was intravenously (i.v.) administered once daily for five consecutive days before enrolling the patients in the long-term oral treatment phase. Both PLA tablets and solutions contained ingredients identical with those containing TA except for the latter. In order to achieve a color similar to the active drug ferrooxide (E 172) was added to the tablets and 0.03 mg of riboflavin to the ampoules.

The study was performed by general practitioners in Germany. Ethical approval was obtained from all regional ethics committees. The electrophysiological measurements were performed by regional neurologists. To be eligible, the patients aged between 18–60 years had to be symptomatic and have evidence of polyneuropathy based on abnormal peripheral nerve function according to clinical and electrophysiological examinations.

Patients with severe neuropathy including paresis, muscle atrophy, severe symptomatic diabetic neuropathy, causes of neuropathies other

than diabetes and other significant neurological diseases were excluded from the study. The use of medications likely to interfere with the interpretation of the results (e.g. γ-linolenic acid, antioxidants, antidepressants, anticonvulsants, mexiletine, neuroleptics, Vitamin B) prevented inclusion.

Peripheral Nerve Function

Neuropathic deficits were assessed using the Neuropathy Disability Score (NDS) described by Young *et al.*[27] Sural sensory nerve conduction velocity (SNCV) and sensory nerve action potential (SNAP) as well as tibial motor nerve conduction velocity (MNCV) and motor nerve distal latency (MNDL) were measured at baseline and after 12 and 24 months. These electrophysiological measurements were performed with surface electrodes at a limb temperature of 33–34°C according to the protocol of Storr and Bluthardt.[26]

Laboratory Measurements

Glycosylated hemoglobin (HbA1c) was determined at baseline and after 6, 12, 18 and 24 months with the HPLC technique using a diamat analyzing system (Bio-Rad, Munich, Germany). Laboratory tests including creatinine, hemoglobin, SGOT, SGPT, gamma GT, alkaline phosphatase, erythrocyte sedimentation rate, leucocytes, platelets, total bilirubin, uric acid, cholesterol, and triglycerides were measured at baseline and after 6, 12, 18 and 24 months.

Statistical Analysis

Continuous variables and their differences from baseline to 24 months were analyzed using descriptive statistical measures including the arithmetical mean, standard deviation, median, quartiles, minimum and maximum. Dichotomous variables were analyzed by contingency tables and pre-post shift tables. For explorative treatment comparisons t-tests for independent samples to analyze the changes from baseline to 24 months between the three groups studied were performed. The level of significance was set at $\alpha = 0.05$. All tests are of descriptive character only and therefore, no α-adjustment was considered. Treatment emergent adverse events were coded according to the WHO/BfArM (Adverse Reaction Terminology) thesaurus and analyzed on preferred term and on body system level.

Data Analysis

A total of 299 patients were recruited from 32 outpatient centers in Germany and randomly assigned to TA 1200, TA 600 or PLA according to their entry sequence following a central computerized randomization list. The initial aim was to use an intention-to-treat statistical analysis of these patients, but major problems were faced even before completion of the study including a high rate of drop-outs ($n = 52$), withdrawal due to concurrent disease ($n = 15$) or adverse events ($n = 3$), protocol violators ($n = 31$) and patients with peripheral vascular disease ($n = 29$). The primary analysis therefore included 169 patients, who had completed the 24 month trial.

Because of major flaws in the electrophysiological assessment in a considerable number of patients, a valid test of the primary hypothesis that TA prevents diabetic polyneuropathy was not possible. Therefore, a secondary subgroup analysis was performed in a cohort of patients from which patients with probably invalid or excessively variable results had been excluded. For this purpose independent clinical neurophysiologists not involved in the study were recruited to act as experts to exclude serial data of patients that they considered to be excessively variable or not plausible. After exclusion by this expert panel only 65 patients could be included in the final analysis (TA 1200 $n = 18$, TA 600 $n = 27$, PLA $n = 20$).

TABLE I Clinical characteristics of patients suitable for analysis at entry

	Placebo	TA 600	TA 1200
Number	20	27	18
Sex (Male/Female)[a]	10/10	11/16	7/11
Age (Years)	57.3 ± 6.4	58.1 ± 17.3	58.0 ± 5.5
Body mass index (kg/m^2)	28.3 ± 3.4	29.2 ± 3.5	29.9 ± 4.0
Systolic blood pressure (mmHg)	137.7 ± 10.5	141.3 ± 17.8	140.6 ± 18.6
Diastolic blood pressure (mmHg)	82.0 ± 7.6	82.4 ± 11.3	83.0 ± 8.9
Smokers[a]	3	7	1
HbA_{1c} (%) at baseline	93 ± 2.2	88 ± 1.5	9.1 ± 2.2
HbA_{1c} (%) after 24 months	9.1 ± 2.4	9.2 ± 2.2	8.0 ± 1.5

Values are mean ± SD or [a]number of patients.

The baseline demographic data of these patients did not differ significantly between the groups for any of the variables listed (Table I).

RESULTS

Glycemic control The HbA_{1C} levels changed from baseline to month 24 from 9.1 ± 2.2% to 8.0 ± 1.5% in TA 1200, from 8.8 ± 1.5% to 9.2 ± 2.2% in TA 600 and from 9.3 ± 2.2% to 9.1 ± 2.4% in PLA. Comparisons of these changes did not show any statistically significant differences between the treatment groups.

Peripheral nerve function At entry into the study, there were no significant differences between the groups for any of the four parameters studied. After 24 months sural SNCV increased significantly (all p-values compared to PLA) in TA 1200 and TA 600 (both $p < 0.05$), sural SNAP in TA 600 ($p < 0.05$) and in TA 1200 ($p = 0.08$). Tibial MNCV increased significantly in TA 1200 ($p < 0.05$). The changes in tibial MNDL did not differ significantly between the three groups after 24 months (Table II).

Furthermore, no significant differences between the three groups were noted for the changes of the NDS from baseline to 24 months (−0.2 ± 2.9 points in TA 1200, −0.19 ± 2.13 points in TA 600, and −0.6 ± 3.1 points in PLA).

Safety monotoring Treatment-emergent adverse events and laboratory tests showed no differences between the groups as it is shown in Table III. Furthermore the global assessment of tolerability was very good and/or good in 100% of the patients in the PLA group, 89% in TA 600 and 94% in TA 1200.

DISCUSSION

In this trial a beneficial and statistically significant effect of TA on several attributes of nerve conduction, particularly sural SNCV, was observed after two years of treatment. The magnitude of improvement in sural SNCV of 3 and 3.8 m/s for 600 and 1200 mg of TA, respectively, appears to signify a clinically meaningful degree of improvement.[28] In addition, it has been demonstrated that 2-year treatment with 600 and 1200 mg of TA is safe, as it did not show significantly more side effects than PLA treatment and was rated at very good/good tolerability by almost all patients. The lack of effect on the NDS is not surprising. First, the number of patients included in the final analysis was too small in view of the purpose of the NDS which was developed as a screening method for epidemiological studies including large groups of patients. Second, finding a favorable effect on nerve conduction but not on deficits is expected, because electrophysiological parameters are considered to be the most

TABLE II Changes of peripheral nerve function indices from baseline to 24 month

	Placebo	TA 600	TA 1200
Sural SNCV (m/s)			
Baseline	41.6 ± 4.1	41.0 ± 7.1	38.9 ± 95
Change (month 24)	−0.1 ± 4.8	3.0 ± 3.0[a]	3.8 ± 4.2[a]
Sural SNAP (μV)			
Baseline	33 ± 3.2	3.1 ± 2.4	25 ± 2.0
Change (month 24)	−0.7 ± 1.5	0.3 ± 1.4[a]	0.6 ± 2.5[b]
Tibial MNCV (m/s)			
Baseline	48.2 ± 6.2	46.6 ± 6.2	47.1 ± 5.1
Change (month 24)	−1.5 ± 2.9	−0.3 ± 5.2	1.2 ± 3.8[a]
Tibial nerve DML (ms)			
Baseline	5.4 ± 1.3	5.1 ± 1.2	5.2 ± 0.9
Change (month 24)	0.0 ± 1.1	−0.03 ± 1.1	−0.17 ± 1.3

Values are mean ± SD, [a]$p < 0.05$ vs PLA, [b]$p = 0.076$ vs PLA.
SNCV: sensory nerve conduction velocity; MNCV: motor nerve conduction velocity; SNAP: sensory nerve action potential; DML: distal motor latency.

objective, sensitive, and reliable measures in the assessment of diabetic polyneuropathy.[29] The results of this trial complement those of previous single-blind pilot and double-blind PLA-controlled studies. In the ALADIN Study Ziegler *et al.* showed an improvement of neuropathic symptoms after three weeks of i.v. treatment with 600 mg of TA.[3] The beneficial effect of 600 mg of TA i.v. on symptoms of diabetic polyneuropathy could be maintained by a subsequent oral therapy using 600 mg of TA over several months.[4] Improvement in cardiac autonomic nerve function was observed in a PLA-controlled double-blind trial after oral treatment over four months using a dose of 800 mg of TA.[25]

The exclusion of a considerable number of patients with records showing excessive variability and probably invalid results as assessed by independent external reviewers requires comment. To the extent that these expert clinical neurophysiologists were blinded as to the treatment group of the case records they excluded, they should not have been biased. However, the initial randomization and intention-to-treat plan could obviously not be adhered to. In addition, the treatment groups were smaller than desirable. Although the primary hypothesis that TA is effective was tested in 169 patients, it was doubtful that this was a valid test of the hypothesis. The analysis of these 169 patients showed no statistically significant changes between TA and PLA, but there was a considerably high variability of the changes in the nerve conduction studies from baseline to 24 months. For example the mean changes and their standard deviations for the tibial MNCV were −1.58 ± 7.19 m/s (TA 1200), −0.87 ± 10.29 m/s (TA 600), and −1.66 ± 7.68 m/s (PLA). The corresponding values for the sural SNAP were 7.86 ± 38.78 μV (TA 1200), 5.71 ± 38.30 μV (TA 600), and 5.58 ± 21.46 μV (PLA). These standard deviations of the changes in the electrophysiological tests from baseline to follow-up were up to 15-fold higher, when compared with those obtained in the final analysis including the group of 65 patients remaining following the external review.

A growing body of evidence suggests that oxidative stress resulting from enhanced free-radical formation and/or defects in antioxidant defence is implicated in the development of various disorders including diabetic complications.[30,31] In experimental diabetic neuropathy, oxygen free radical activity in the sciatic nerve is increased.[13,32] Treatment with TA as a potent lipophilic free-radical scavenger, results in prevention of the neurovascular abnormalities

TABLE III Treatment emergent adverse events by body systems

Body system level/Who preferred terms	T 1200 ($n = 101$)	T 600 ($n = 100$)	PLA ($n = 105$)
Skin and appendages disorders			
Pruritus	3	1	3
Skin ulceration	2	5	2
Musculo-skeletal system disorders			
Arthralgia	5	6	8
Arthrosis	3	5	3
Back pain	9	19	18
Centr. and periph. nervous system disorders			
Cramps legs	1	4	5
Dizziness	7	2	6
Headache	16	11	12
Paraesthesia	2	3	1
Autonomic nervous system disorders			
Glaucoma	1	3	2
Hypertension	2	4	2
Vision disorders			
Glaucoma	1	3	2
Vision abnormal	2	0	5
Psychiatric disorders			
Sleep disturbances	1	4	2
Gastro-Intestinal system disorders			
Abdominal pain	10	5	7
Constipation	3	1	1
Diarrhoea	3	5	7
Dyspepsia	6	5	3
Flatulence	3	2	4
Gastritis	1	4	4
Nausea	7	4	2
Tooth ache	4	3	4
Metabolic and nutritional disorders			
Hyperlipaemia	2	2	6
Cardiovascular disorders			
Hypertension	2	4	2
Myo endo pericardial and valve disorders			
Angina pectoris	6	9	5
Heart rate and rhythm disorders			
Arrhythmia	2	4	1
Vascular (extracardiac) disorders			
Cramps legs	1	4	5
Respiratory sytem disorders			
Bronchitis	15	12	9
Coughing	2	1	3
Pharyngitis	4	1	9
Sinusitis	4	2	1
Upper resp. tract infection	4	4	5
Urinary system disorders			
Urinary tract infection	2	2	3
Body as a whole – general disorders			
Influenza-like symptoms	16	18	19
Pain	6	7	8
Resistance mechanism disorders			
Infection	3	6	2

associated with experimental diabetic neuropathy.[20] It has been demonstrated that reduced digital nerve conduction velocity (NCV), nerve blood flow, and glutathione levels in diabetic rats are normalized and *in vitro* lipid peroxidation of neural tissue is reduced by TA in a dose-dependent manner,[19,20] suggesting that the improvement in neurovascular changes were induced by improving oxygen free-radical scavenging activity. One mechanism of reduced nerve blood flow is the inhibitory effect of superoxide anion on vasodilatation by scevenging nitric oxide. Since nitric oxide synthase is reduced in experimental diabetic neuropathy,[33] TA might prevent this inhibition by reducing oxidative stress. A recent study has also demonstrated that treatment with TA may correct deficits in neuropeptides (neuropeptide Y- and substance P-like activity) in spinal cord of diabetic rats, indicating that the compound may boost neurotrophic support.[23] Furthermore, TA has been shown to increase myocardial glucose uptake/utilization and cardiac output,[34] enhance endoneurial glucose uptake, energy metabolism, and myo-inositol content,[35] improve neural or endothelium-mediated relaxation in the corpus cavernosum,[36] prevent dysfunction of endothelium-dependent hyperpolarizing factor (EDHF) and NO systems in the mesenteric vasculature,[37] partially prevent diabetes-induced impairments of antioxidative defense, glucose intermediary metabolism via glycolysis, and energy status in lens,[38] and to increase the NAD^+/NADH ratio, superoxide dismutase, and catalase activities in sciatic nerve.[39] Administration of low doses of TA/γ-linolenic acid conjugate corrects the nerve conduction and nerve blood flow deficits[40] as well as sciatic nerve contents of nerve growth factor, substance P, and neuropeptide Y[41] in diabetic rats, suggesting a synergistic action of these compounds. Another mode of action of α-lipoic acid in the experimental setting includes a suppression of the activation of the free radical-sensitive transcription factor NF-κB in cultured endothelial cells.[42] Interaction of advanced glycation end products (AGEs) with their endothelial surface receptors (RAGEs) generates intracellular oxidative stress, resulting in activation of NF-κB which translocates into the nucleus and induces the expression of endothelial gene products such as endothelin-1 and tissue factor that are increased in diabetes.[42] Such a protection of cellular antioxidative defense mechanisms by α-lipoic acid that prevents endothelial dysfunction *in vitro* via suppression of NF-κB activation could also be relevant in the diabetic nerve. In a preliminary study 3-day oral treatment with 600 mg of TA reduced NF-κB activation in peripheral blood mononuclear cells that was paralleled by a decrease in oxidative stress in plasma of diabetic patients with nephropathy.[43] Other recent studies in Type 2 diabetic patients indicate that i.v. or oral treatment with TA for several days or weeks may improve insulin sensitivity,[44,45] glucose effectiveness,[46] and parameters of increased oxidative stress.[47] Thus, there is abundant evidence from experimental studies suggesting a major pathogenetic role of oxidative stress in diabetic neuropathy.

In conclusion, the present results along with those of the recent studies using appropriately high doses of TA ($\geq$ 600 mg per day) indicate that 2-year treatment may exert favorable effects on peripheral nerve function in diabetic patients with polyneuropathy. It is of particular interest that no significant adverse reactions in association with the drug were observed in this long-term treatment. To further substantiate the results of the aforementioned studies a large scale controlled phase III trial (NATHAN 1) is being conducted in North America and Europe according to the recommendations of the Peripheral Nerve Society.[29]

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