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α-Lipoic acid as a new treatment option for Alzheimer's disease – a 48 months follow-up analysis

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Summary Oxidative stress and neuronal energy depletion are characteristic biochemical hallmarks of Alzheimer's disease (AD). It is therefore conceivable that pro-energetic and antioxidant drugs such as α-lipoic acid might delay the onset or slow down the progression of the disease. In a previous study, 600 mg α-lipoic acid was given daily to nine patients with AD (receiving a standard treatment with choline-esterase inhibitors) in an open-label study over an observation period of 12 months. The treatment led to a stabilization of cognitive functions in the study group, demonstrated by constant scores in two neuropsychological tests (the mini mental state exam, MMSE and the Alzheimer's disease assessment score cognitive subscale, ADAScog). In this report, we have extended the analysis to 43 patients over an observation period of up to 48 months. In patients with mild dementia (ADAScog < 15), the disease progressed extremely slowly (ADAScog: $+1.2$ points/year, MMSE: -0.6 points/year), in patients with moderate dementia at approximately twice the rate. However, the progression appears dramatically lower than data reported for untreated patients or patients on choline-esterase inhibitors in the second year of long-term studies. Despite the fact that this study was not double-blinded, placebo-controlled and randomized, our data suggest that treatment with α-lipoic acid might be a successful 'neuroprotective' therapy option for AD. However, a state-of-the-art phase II trial is needed urgently.

Keywords: Dementia, Alzheimer's disease, lipoic acid, neuroprotection, open clinical trial

Introduction

Peter Riederer has proposed for more than 20 years that oxidative stress is a major cause of cell death in Parkinson's and Alzheimer's disease (AD). He and his co-workers proposed that a gradual impairment of cellular defense mechanisms leads to cell damage including accumulation of advanced glyction endproducts because of toxic substances e.g. superoxide from mitochondrial respiration being increasingly formed during normal cellular metabolism. This point of view brings into consideration the possibility that, besides exogenous factors, the pathogenetic process of neurodegeration is triggered by endogenous mechanisms, either by an endogenous toxin or by inherited metabolic disorders, which become progressively more evident with aging (Frölich and Riederer, 1995; Götz et al., 1994; Retz et al., 1998; Rösler et al., 1998). AD is on of the most likely diseases involving oxidative stress as a causative pathogenic factor which occurs earlier than the pathological hallmarks of the disease, amyloid plaques and neurofibrillary tangles (Perry et al., 1998). Besides oxidative stress, neuronal energy depletion is a second characteristic biochemical hallmarks of AD (Münch et al., 1998). It is therefore conceivable that pro-energetic and antioxidants such as α-lipoic acid might delay the onset or slow down the progression of the disease (Holmquist et al., 2006).

We have previously conducted a small pilot study with 9 patients over a period of nine months showing some indication that α-lipoic acid may fulfil this therapeutic need (Hager et al., 2001). A naturally-occurring precursor of an essential cofactor for mitochondrial enzymes, including pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, α-lipoic acid has been shown to have a variety of properties which can interfere with pathogenic principles of AD. For example, α-lipoic acid increases acetylcholine production by activation of choline acetyltransferase and increases glucose uptake, thus supplying more acetyl-CoA for the production of acetylcholine. α-Lipoic acid chelates

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redox-active transition metals, thus inhibiting the formation of hydroxyl radicals and also scavenges reactive oxygen species (ROS), thereby increasing the levels of reduced glutathione (Packer et al., 1995). Via the same mechanisms, downregulation redox-sensitive inflammatory processes can also be achieved (Wong et al., 2001). Furthermore, α-lipoic acid can scavenge lipid peroxidation products such as hydroxynonenal and acrolein. The reduced form of α-lipoic acid, hydrolipoic acid (DHLA), is the active compound responsible for most of these beneficial effects. R-α-lipoic acid can be applied instead of DHLA, as it is reduced by mitochondrial lipoamide dehydrogenase, a part of the pyruvate dehydrogenase complex (Biewenga et al., 1997). In this study, cognitive functions of 43 AD patients treated with α-lipoic acid for periods up to 4 years were analyzed.

Patients and methods

The study was designed as an open, non-randomized investigation of outpatients presented at the memory clinic with an initial diagnosis of probable Alzheimer's disease. Subjects underwent an evaluation using clinical interview, mental status assessment, physical and neurological examinations. All participants met the criteria of DSM-III-R (APA, 1987) for probable AD. Subjects were required to be aged 45 years or older upon the first signs of memory complaint, and have a closely related caregiver (spouse, parent or child). Patients with a history suggesting a familial form of AD were excluded. Informed consent was obtained from each subject, the caregiver or the legal guardian. The study was approved by the institutional review board. Patients received the standard treatment of an choline-esterase inhibitor at least 3 months prior to starting the α-lipoic acid treatment, which was given once daily in a dose of 600 mg, administered in the morning, 1 h before breakfast. For assessing cognitive performance, the mini-mental state examination (MMSE) and the cognitive subscale of the AD assessment scale (ADAS-cog) were applied (Storey et al., 2002). Between 1998 and 2004, 43 patients – divided in three groups according to the severity of their dementia – were included in the study (Table 1).

Results

The patients included in our study were tested by means of MMSE and ADAScog prior to and several times (in most cases every 6 months) after the start of the treatment with 600 mg daily of α-lipoic acid up to a total of 48 months. Before starting treatment with α-lipoic acid, despite cognitive training as well as treatment with acetylcholinesterase inhibitors, the test results showed a constant decline. Test results for the moderate-advanced group could only be obtained for 2.5 years because the patients increasingly were admitted to nursing homes where medication and testing was discontinued after that period. As expected for an irreversible disease as AD, all three patient groups showed a steady decline of the cognitive functions but the decline in the α-lipoic acid treated patients appears to be much slower compared to may other studies published in the current literature. Similar to other observations in the literature, cognitive decline was slower in the early stages of the disease, as the mild AD group showed the slowest degree of decline (MMSE: −0.6 points per year) compared to the other groups (MMSE: −1.4 points per year) (Table 2, Fig 1). It has to be noticed that for the mild and the early moderate patient group, the progression rate slows down after 3 years. However, this is rather caused by the selection of the ''slow decliners'' than an overall slowdown of disease progression. In summary, α-lipoic acid showed some promising effects in this larger study supporting our previous data but we are cautious with a too positive interpretation of the data because of the open design of the study.

Table 1. *Characteristics of the study population*

Patients group	Number of patients on LS treatment	Age (years)	Type of choline-esterase inhibitor	Time between start of choline-esterase inhibitor and LS treatment (days)	Period of data collection (years)
Mild dementia	Start: 12 1 yr: 12 2 yrs: 11 3 yrs: 7 4 yrs: 7	65.0 ± 12.6	Aricept: 7 Reminyl: 3 no choline-esterase inhibitors: 2	411 ± 341	4
Moderate-early dementia	Start: 19 1 yr: 19 2 yrs: 16 3 yrs: 13 4 yrs: 9	63.0 ± 7.4	Aricept: 15 Reminyl: 4	436 ± 406	4
Moderate-advanced dementia	Start: 12 1 yr: 12 2 yrs: 5 2 yrs: 3	69.5 ± 8.7	Aricept: 10 Reminyl: 2	638 ± 509	2.5

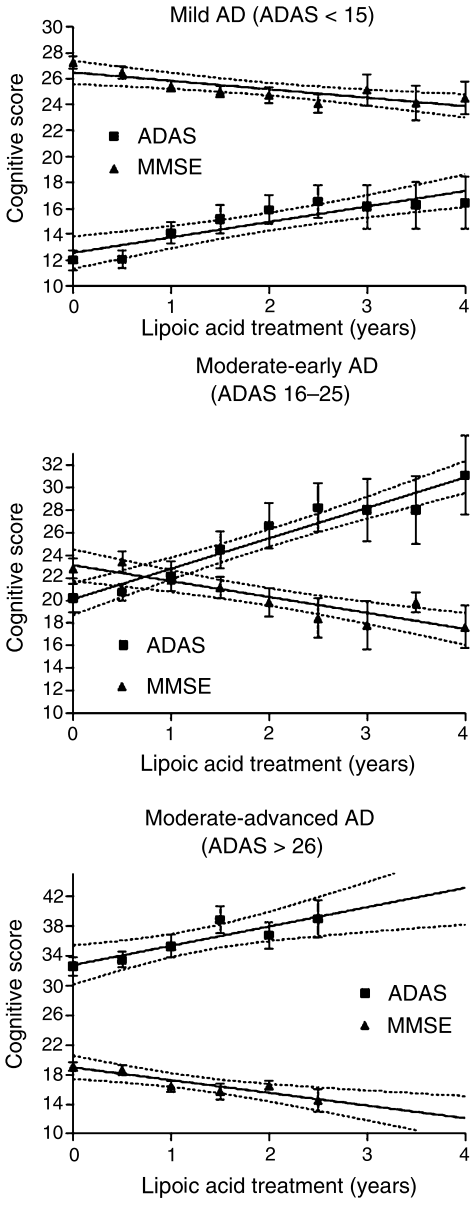

Fig. 1. Time-dependent changes in MMSE (triangles) and ADAScog scores (squares) in patients (divided into subgroups according to severity) treated with α-lipoic acid over an observation period of up to 4 years. Data are presented as mean ± SEM

Discussion

The natural history of Alzheimer's disease is one of progressive decline; cognitive, physical, and social functions gradually deteriorate. Thus, ''improvement'' from an intervention for Alzheimer's disease means slowing the rate of decline. The rate of decline in Alzheimer's disease is not linear, however. People with mild dementia (ADAScog < 15) experience an average rate of decline of 5 or fewer ADAScog points (2 or fewer MMSE points) per year. By contrast, those individuals with moderate dementia (ADAScog >15 but <55) experience an average decline in cognition of 7–11 ADAScog points (2–4 MMSE points) annually (Stern et al., 1994). With a decrease of less that two points in the MMSE and an increase of less than three points in the ADAScog per year, the decline of the lipoic acid treated patients was relatively small compared to data from the literature (Table 3), indicating that lipoic acid slows down the progression of dementia. The slow decline is unlikely the consequence of the choline-esterase inhibitors treatment for two reasons: a) the majority of patients started choline-esterase inhibitors treatment several months before entering the LS study and b) the slower decline continued beyond the first year of the study where usually the positive effects of choline-esterase inhibitors level off (AD2000 Collaborative Group, 2004). However, our open trial is open to a biased selection of patients. It is conceivable that patients or caregivers willing to try novel therapies are more likely to try other beneficial lifestyle changes such as nutritional approaches and physical and mental exercise as well. On the other hand, patients whose disease progresses rapidly despite the standard therapies with choline-esterase inhibitors might particularly ask for α-lipoic acid as the ''drug of last resort'' and our study would particularly attract the more rapid decliners. In summary, our data suggest that a pro-energetic and antioxidant drug such as α-lipoic acid might delay the onset or slow down the progression of the disease, and we are confident that our results will encou-

Table 2. *Time-dependent changes in cognitive scores of α-lipoic acid treated patients*

Patient group	ADAScog scores (at start LS treatment)	Increase in ADAScog scores per year	MMSE scores (at start LS treatment)	Decrease in MMSE scores (per year)
Mild dementia (ADAS 0–15)	12.0 ± 2.7	1.2 ± 0.2 (2.0 ± 0.2 in the first 30 months)	27.3 ± 1.7	0.6 ± 0.2 (1.2 ± 0.1 in the first 30 months)
Moderate-early dementia (ADAS 16–25)	20.2 ± 5.5	2.7 ± 0.2 (3.4 ± 0.3 in the first 30 months)	22.8 ± 3.4	1.4 ± 0.2 (1.6 ± 0.2 in the first 30 months)
Moderate-advanced dementia (ADAS > 26)	32.6 ± 4.3	2.6 ± 0.2	19.1 ± 2.1	1.4 ± 0.4

Table 3. *Time-dependent decline in cognitive scores – comparison with published studies*

ADAS				
ADAScog scores of our patient group (at start LS treatment)	Change in ADAScog in our patient group per year	ADAScog scores of comparative patient group at start	Change in ADAScog in comparative patient group per year	Study information
12.0 (mild)	$+1.2 \pm 0.2$ (2.0 in the first 30 months)	<15	approx. 5	untreated AD patients (Stern et al., 1994)
		18 (9.4) hydroxychloroquine and 17.6 (9.1) placebo	estimated 5.6 (5.9) and 5.4 (6.8), respectively	randomised double-blind trial with 168 AD patients for 18-month (Van Gool, 2001)
20.2 (moderate-early)	$+2.7 \pm 0.2$ (3.4 ± 0.3 in the first 30 months)	21.8	4.4 (0–3 years) 6.5 (1st–3rd years)	open label trial with 4–6 mg rivastigmine for up to 5 years (Farlow et al., 2005)
		20	6	Mohs (1996)
32.6 (moderate-advanced)	$+2.6 \pm 0.2$	40	13	Mohs (1996)
		60	7	Mohs (1996)
MMSE				
MMSE scores of our patient group (at start LS treatment)	Change in MMSE in our patient group per year	MMSE scores of comparative patient group at start	Change in MMSE in comparative patient group per year	Study information
27.3 (mild)	-0.6 ± 0.2	n/a (i.e. many clinical trials in AD restrict MMSE entry scores to 10–25)	n/a	MMSE is less sensitive for patients with mild cognitive impairment (Galasko et al., 2000)
		approx. 26	approx. −4.4	course of decline was studied in 16 AD patients for up to 5 years (Haxby et al., 1992)
		23.7 ± 2.4	-3.9 ± 4.1	1 year, multicenter (27) evaluation, in an AD cooperative study/USA (Ferris et al., 1997)
22.8 (moderate-early)	-1.4 ± 0.2	19.26 ± 4.54, 19.37 ± 4.37 (range 10–26)	−2.3 without or −0.5 with donezepil	randomised double-blind trial with 286 AD patients for 1 year (Winblad et al., 2001)
		23 ± 3.9	−2.3	Study investigating the rate of progression, 54 AD patients (Rascovsky et al., 2005)
		mean ranged from 7.2 to 26 (median: 18.4)	−3.3	meta-analysis of 37 studies, 3492 AD patients, over an average of 2 years (Han et al., 2000)
19.3 (moderate-advanced)	-1.4 ± 0.4	19.0	−3 without or −2.4 with donezepil	randomised double-blind trial with 565 AD patients for 2 years (AD2000 Collaborative Group, 2004)
		mean ranged from 7.2 to 26 (median: 18.4)	−3.3 (95% CI: 2.9–3.7)	meta-analysis of 37 studies, 3492 AD patients, over an average of 2 years (Han et al., 2000)
		18.5 ± 4.6	approx. −2.81	longitudinal evaluation of 3 mental status examinations, 92 AD patients (Salmon et al., 1990)

rage the initiation of a state-of-the-art phase II clinical trial.

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References

AD2000 Collaborative Group (2004) Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet 363: 2105–2115

Biewenga GP, Haenen GR, Bast A (1997) The pharmacology of the antioxidant lipoic acid. Gen Pharmacol 29: 315–331

Farlow MR, Lilly ML, Group EBS (2005) Rivastigmine: an open-label, observational study of safety and effectiveness in treating patients with Alzheimer's disease for up to 5 years. BMC Geriatrics 5: 3

Ferris SH, Mackell JA, Mohs R, Schneider LS, Galasko D, Whitehouse PJ, Schmitt FA, Sano M, Thomas RG, Ernesto C, Grundman M, Schafer K, Thal LJ (1997) A multicenter evaluation of new treatment efficacy instruments for Alzheimer's disease clinical trials, overview and general results. Alzheimer Dis Assoc Disord 11: Sl–S12

Frölich L, Riederer P (1995) Free radical mechanisms in dementia of Alzheimer type and the potential for antioxidative treatment. Arzneimittelforschung 45: 443–446

Galasko DR, Gould RL, Abramson IS, Salmon DP (2000) Measuring cognitive change in a cohort of patients with Alzheimer's disease. Stat Med 19: 1421–1432

Götz ME, Kunig G, Riederer P, Youdim MB (1994) Oxidative stress: free radical production in neural degeneration. Pharmacol Ther 63: 37–122

Hager K, Marahrens A, Kenklies M, Riederer P, Münch G (2001) Alpha-lipoic acid as a new treatment option for Alzheimer type dementia. Arch Gerontol Geriatr 32: 275–282

Han L, Cole M, Bellavance F, McCusker J, Primeau F (2000) Tracking cognitive decline in Alzheimer's disease using the Mini-Mental State examination: a meta-analysis. Int Psychogeriatr 12: 231–247

Haxby JV, Raffaele K, Gillette J, Schapiro MB, Rapoport SI (1992) Individual trajectories of cognitive decline in patients with dementia of the Alzheimer type. J Clin Exp Neuropsychol 14: 575–592

Holmquist L, Stuchbury G, Berbaum K, Muscat S, Young S, Hager K, Engel J, Munch G (2006) Lipoic acid as a novel treatment for Alzheimer's disease and related dementias. Pharmacol Ther 113: 154–164

Mohs RC (1996) Comprehensive and neuropsychologic evaluations: the Alzheimer's disease assessment scale. Int Psychogeriatr 8: 195–203

Münch G, Schinzel R, Loske C, Wong A, Durany N, Li JJ, Vlassara H, Smith MA, Perry G, Riederer P (1998) Alzheimer's disease – synergistic effects of glucose deficit, oxidative stress and advanced glycation endproducts. J Neural Transm 105: 439–461

Packer L, Witt EH, Tritschler HJ (1995) alpha-Lipoic acid as a biological antioxidant. Free Radic Biol Med 19: 227–250

Perry G, Castellani RJ, Hirai K, Smith MA (1998) Reactive oxygen species mediate cellular damage in Alzheimer disease. J Alzheimers Dis 1: 45–55

Rascovsky K, Salmon DP, et al. (2005) Rate of progression differs in frontotemporal dementia and Alzheimer disease. Neurology 65: 397–403

Retz W, Gsell W, Münch G, Rösler M, Riederer P (1998) Free radicals in Alzheimer's disease. J Neural Transm Suppl 54: 221–236

Rösler M, Retz W, Thome J, Riederer P (1998) Free radicals in Alzheimer's dementia: currently available therapeutic strategies. J Neural Transm Suppl 54: 211–219

Stern R, Mohs R, Davidson M, Schmeidler J, Silverman J, Kramer-Ginsberg E (1994) A longitudinal study of Alzheimer's disease: measurement, rate, and predictors of cognitive deterioration. Am J Psychiatry 151: 390–396

Storey E, Slavin MJ, Kinsella GJ (2002) Patterns of cognitive impairment in Alzheimer's disease: assessment and differential diagnosis. Front Biosci 7: e155–e184

Van Gool AW, Weinstein HC, Scheltens P, Walstra GJ (2001) Effect of hydroxychloroquine on progression of dementia in early Alzheimer's disease: an 18-month randomised, double-blind, placebo-controlled study. Lancet 358: 455–460

Winblad B, Engedal K, et al. (2001) A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. Neurology 57: 489–495

Wong A, Dukic-Stefanovic S, Gasic-Milenkovic J, Schinzel R, Wiesinger H, Riederer P, Münch G (2001) Anti-inflammatory antioxidants attenuate the expression of inducible nitric oxide synthase mediated by advanced glycation endproducts in murine microglia. Eur J Neurosci 14: 1961–1967