PHARMACOLOGICAL TREATMENT OF DIABETIC NEUROPATHY: α-LIPOIC ACID

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A substantial body of evidence suggests that oxidative stress resulting from enhanced free-radical formation and/or defects in antioxidant defence plays a major role among the putative pathogenic mechanisms of diabetic neuropathy. Consequently, antioxidants such as α-lipoic acid (thioctic acid) have been shown to improve experimental diabetic neuropathy. Multiple randomized clinical trials using α-lipoic acid in diabetic neuropathy have been published. To obtain an overall picture regarding the efficacy of α-lipoic acid using 600 mg i.v. per day for 3 weeks (without treatment on weekends) in symptomatic diabetic sensorimotor polyneuropathy (DSPN), four comparable randomized placebo-controlled double-blind studies (ALADIN, ALADIN III, SYDNEY, NATHAN II) were subjected to a meta-analysis (1). Primary analysis involved a comparison of the differences in the total Symptom Score (TSS) from baseline to the end of i.v. treatment between the groups treated with α-lipoic acid or placebo. In total, 1258 patients were included in the analysis (α-lipoic acid: n=716; placebo: n=542). After 3 weeks, the relative difference in favor of α-lipoic acid vs. placebo was 24.1% (95% CI: 13.5-33.4%) for TSS and 16.0% (5.7-25.2%) for NIS-LL. The responder rates were 52.7% in patients treated with α-lipoic acid and 36.9% in those on placebo (P<0.05). Among the individual components of the TSS, pain, burning, and numbness decreased in favor of α-lipoic acid compared with placebo, while among the NIS-LL components pin-prick and touch-pressure sensation as well as ankle reflexes were improved in favor of α-lipoic acid after 3 weeks. The rates of adverse events did not differ between the groups. The results of this meta-analysis demonstrate at the highest evidence level (Evidence Class Ia) that treatment with α-lipoic acid (600 mg/day i.v.) over 3 weeks is safe and significantly improves both positive neuropathic symptoms and neuropathic deficits to a clinically meaningful degree in diabetic patients with symptomatic DSPN.

Two recently published independent meta-analyses confirm these findings and provide the following valuations. The first meta-analysis comprised data from 1160 participants in the ALADIN, SYDNEY, ORPIL, SYDNEY 2, and ALADIN III studies. Analysis included studies with a level of evidence of at least 2b. In four of the studies, α-lipoic acid provided significant improvement in manifestations of DSPN. In conclusion, treatment with α-lipoic acid 600 mg i.v. daily for 3 weeks represents a well-tolerated and effective therapy for DSPN. An oral dose of 600 mg daily administered for up to 5 weeks could offer benefits in symptoms and signs of DSPN without significant side effects (2).

The second meta-analysis is a systematic review of randomized controlled studies using the TSS as endpoint. Overall, the pooled standardized mean difference estimated from 4 trials revealed a reduction in TSS scores of −2.26 (95% CI: −3.12 to −1.41; P=0.00001) in favor of α-lipoic acid administration. Subgroup analyses of oral administration from 2 trials (−1.78 CI: −2.45 to −1.10; P=0.00001) and i.v. administration from 2 trials (−2.81 CI: −4.16 to −1.46; P=0.0001) confirmed the robustness of the overall result. In conclusion, when given i.v. at a dosage of 600 mg/day over a period of 3 weeks, α-lipoic acid leads to a significant and clinically relevant reduction in neuropathic pain (grade of recommendation A) (3).

References

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