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 COMMENTS AND  
 RESPONSES
 

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**Comment on: Fraser et al. The Effects of Long-Term Oral Benfotiamine Supplementation on Peripheral Nerve Function and Inflammatory Markers in Patients With Type 1 Diabetes: A 24-Month, Double-Blind, Randomized, Placebo-Controlled Trial. Diabetes Care 2012;35:1095–1097**

Fraser et al. (1) reported that “high-dose benfotiamine (300 mg/day) supplementation over 24 months has no significant effects upon peripheral nerve function or soluble markers of inflammation in patients with type 1 diabetes.” Although this conclusion may be correct based on these findings, the clinical relevance remains obscure in view of the questionable study design. According to the recent consensus statement of the Toronto Diabetic Neuropathy Expert Group (2), a possible diabetic sensorimotor polyneuropathy (DSPN) can be diagnosed if symptoms or signs of DSPN are present. In the case of probable DSPN, a combination of symptoms and signs of neuropathy is present. The authors state that among the patients included, 56% had subclinical neuropathy based on abnormal nerve conduction studies (NCS), and 16% had probable DSPN. Unfortunately, how abnormal NCS was defined is unclear. In fact, this high percentage is surprising given that mean sural sensory nerve conduction velocity (NCV),

which is one of the most sensitive indicators of DSPN, was well within the normal range. Moreover, clinical neuropathy scores have been used to assume probable DSPN, but obviously the latter has not been confirmed by abnormal NCS. Because the number of subjects included with confirmed DSPN was presumably very low, this trial does not provide any information on the important question as to whether treatment with benfotiamine may improve DSPN or slow its progression. The authors note that in previous studies using benfotiamine, no effect on NCV was shown. In the study by Stracke et al. (3) cited by the authors, improvement in peroneal motor NCV in diabetic patients with DSPN was documented.

Further drawbacks of this trial are the lack of an intention-to-treat analysis to confirm the per protocol data and of an a priori–specified clinically meaningful difference in peroneal motor NCV between the two groups studied.

Recently, it has been suggested that the progression of DSPN in the placebo group within the setting of a randomized clinical trial over 4-year period was slow. Thus, for demonstration of efficacy, trials using drugs for treatment of DSPN must achieve a clinically relevant neurological improvement (4). Unfortunately, the study conducted by Fraser et al. (1) in patients with almost normal nerve function does not leave any room for a meaningful degree of improvement.

The title reads “Benfotiamine Supplementation,” but the dose applied (300 mg/day) was much higher than the recommended daily adult allowance for thiamine (1.4 mg/day). Hence, this was pharmacotherapy rather than vitamin supplementation.

Finally, as far as it can be judged from the article, the patients examined had no chronic inflammation. Therefore, it was foreseeable that no effect on inflammatory markers was shown. In conclusion, it is not surprising that 2-year treatment with benfotiamine versus placebo did not result in meaningful differences between the groups in nerve function or markers of inflammation in patients without evidence of neuropathy nor inflammation. Only trials using appropriate study

designs and end points can assess the effects of benfotiamine on nerve dysfunction resulting from DSPN.

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