COMMENTS AND RESPONSES

Response to 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

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We welcome the commentary of Ziegler et al. (1) and are delighted to have the opportunity to clarify certain details of the study that were included in our first submission but had to be omitted because of article length restrictions.

We don't agree with the statement that because the number of subjects included with confirmed diabetic sensorimotor polyneuropathy (DSPN) was presumably low, our trial does not provide information on whether benfotiamine may improve or slow progression of DSPN. We found that nerve conduction study (NCS) parameters deteriorated in both groups at the same speed/level as found in earlier publications for type 1 diabetes (2). Abnormal nerve conduction score was defined as one or more abnormal *Z* scores in two or more nerves, based on sural nerve amplitude, tibial and peroneal nerve conduction velocity (NCV), tibial amplitude, increased F-wave minimum latency, or absent F-waves. The increase in the number of subjects with abnormal NCS (from 53 to 64%) clearly indicates that a percentage of patients classified as "normal" at baseline were borderline. Four patients in the benfotiamine group went from normal to abnormal NCS during the study whereas only one patient in the placebo group deteriorated. Unfortunately, subgroup analysis of only those patients with abnormal *Z* scores at baseline also failed to show any positive effect of benfotiamine.

Ziegler et al. question our statement that previous studies with benfotiamine haven't shown effect upon NCV and further state that "[o]nly trials using appropriate study designs and end points can assess the effects of benfotiamine on nerve dysfunction resulting from DSPN." We are therefore somewhat surprised that Ziegler et al. cite the 12-week placebo controlled study in 24 diabetic patients of Stracke et al. (3) as evidence suggesting that benfotiamine improves NCV in diabetic patients. In fact, this study had three components in the active arm: benfotiamine, cyanocobalamin, and pyridoxine hydrochloride (at >2 times the dose of benfotiamine). Thus the specific effects of benfotiamine cannot be isolated. Furthermore, placebo group mean peroneal NCV declined markedly from 43.1 to 40.37 m/s in only 12 weeks. Significance in group comparisons may therefore be associated with the marked NCV decline in the placebo group rather than an improvement in the active group in this study.

Regarding the claim that a lack of intention-to-treat is a drawback of our study, intention-to-treat findings mirrored the per-protocol findings but were excluded from the final version because of publication restrictions.

We fully agree that our study used pharmacological doses. Ziegler et al. state that the patients examined had no inflammation. Although it has been shown by Ziegler and colleagues (4) that patients with diabetic polyneuropathy have subclinical inflammation, we accept that we cannot be certain that patients in our study had levels of inflammatory markers above normal because we did not have a healthy control group

In conclusion, we maintain that the findings from our study are robust and not only show a lack of effect of benfotiamine on diabetic polyneuropathy over 2 years, but instead indicate a trend toward deterioration.

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References

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