OBSERVATIONS

Inhibition of IL-1β Improves Fatigue in Type 2 Diabetes

Several diseases including microbial infection, rheumatoid arthritis, multiple sclerosis, and cancer have been linked to fatigue. They all have in common an upregulation of cytokines, including interleukin (IL)-1β and tumor necrosis factor-α (TNF-α), which may interfere with clock gene functions (1). Increasing evidence associates type 2 diabetes with inflammatory processes characterized by elevated production of proinflammatory cytokines and infiltration of immune cells. Reducing IL-1 activity in prediabetes and diabetes improves insulin secretion, glycemic control, and markers of systemic inflammation (2–4). Given this background, we hypothesized that fatigue levels may be increased in type 2 diabetes and may be improved by IL-1β antagonism.

Within a placebo-controlled, double-blind study of IL-1β antagonism with a monoclonal anti–IL-1β antibody, XOMA052, involving 30 patients with type 2 diabetes (4), we evaluated fatigue using the Fatigue Scale for Motor and Cognitive functions (5). Besides differentiating between cognitive and motor fatigue, this scale offers a subdivision into different grades of fatigue severity.

At baseline, according to predefined cutoff values, 47% of the patients had no, 20% had mild, 17% had moderate, and 16% had severe fatigue, meaning that more than half of the patients suffered from considerable fatigue symptoms compared with a healthy population (5). A significant correlation between fatigue and duration of diabetes was evident ($R = 0.532$, $P = 0.002$). This correlation was stronger for cognitive fatigue ($R = 0.541$, $P = 0.002$) compared with motor fatigue ($R = 0.486$, $P = 0.007$). No correlation between fatigue and age, HbA_{1c}, body weight, body temperature, and C-reactive protein was found. One month after treatment with XOMA052, a univariate ANOVA with the pre- and 1 month post-medication difference on total fatigue as the dependent variable and dosage as the fixed factor revealed that in the placebo and the lowest dose group (0.01 mg/kg), fatigue was slightly increased; in the two medium dose groups (0.03 mg/kg and 0.1 mg/kg), fatigue was slightly decreased; and in the two highest dose groups (0.3 mg/kg and 1.0 mg/kg), fatigue was decreased remarkably. The effect size for this dose-dependent effect was $d = 0.3$. When assessing the motor and cognitive function separately, a nonparametric analysis of pre- and 1 month post-medication effects revealed a meaningful trend ($P = 0.07$) on decrease in motor fatigue for patients under the dosage of 1.0 mg/kg of XOMA052. To further evaluate these findings with respect to the small group sizes, effect sizes for pre- and 1 month post-medication comparisons were calculated. Here it could be confirmed with an effect size of $d = 1.05$ that a dosage of 1.0 mg/kg of monoclonal anti–IL-1β antibody had a favorable effect on motor fatigue.

To our knowledge, this is the first study assessing fatigue in diabetes by means of a validated fatigue instrument. It shows that type 2 diabetic patients are more prone to fatigue than normal healthy individuals with a prevalence of more than 50%. Fatigue seems to be correlated with duration of diabetic disease but not with the extent of glycemia or C-reactive protein levels. Moreover, fatigue seems to partly improve following IL-1β blockade.

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