COMMENTS AND RESPONSES

Etanercept Treatment in Children With New-Onset Type 1 Diabetes: Pilot Randomized, Placebo-Controlled, Double-Blind Study

Response to Peters

We thank Dr. Peters (1) for his thoughtful comments regarding our study (2). Dr. Peters suggests that etanercept may effect the partial remission period of type 1 diabetes by mediating declines in autoantibodies, GAD-65 in particular. Clinical data supports the concept that titer and number of autoantibodies correlates with accelerated β-cell demise and a lower likelihood of clinical remission compared with individuals who tested negative for diabetes-associated autoantibodies (3). Changes in GAD-65 antibody levels were not an outcome measure for our study. However, reported herein are the data in subjects whose GAD-65 antibody levels were measured at baseline, week 24 (end of treatment period), and week +12 (washout visit). Based on reported interassay coefficients of variation (3), GAD-65 levels were defined as changed if the value varied 10% or more from baseline. A trend toward declining GAD-65 levels in the etanercept versus placebo group (66% vs. 33%, $n = 6$ for each group) was observed at week 24, but not at week +12. While this observation supports Dr. Peters' hypothesis, the small sample size limits statistical analysis.

We would argue that potential changes in GAD-65 autoantibody levels do not preclude the hypothesis that the primary mechanism of action of etanercept in improving β-cell function is through tumor necrosis factor-α (TNF-α) blockade. In fact, TNF-α blockade is proposed as the rationale for improved diabetes control in patients receiving adalimumab for the treatment of rheumatoid arthritis (4). The role of TNF-α in the development and progression of type 1 diabetes is multifactorial (5). TNF-α can regulate tolerance of T-cells to β-cell autoantigens, including GAD-65. Therefore, any decline in GAD-65 levels seen in etanercept-treated subjects may be the result of decreased GAD-65 autoantibody secreting T-cells mediated by TNF-α blockade. While this is speculative and cannot be addressed by our study, future immunomodulatory trials may examine the effects of these therapies on immune cells that contribute to insulin-producing β-cell demise.

LUCY MASTRANDREA, MD, PHD[1,2]
JIHNHEE YU, PHD[3]
TORSTEN BEHRENS, MA[1]
JOHN BUCHLIS, MD[1,2]
CHRISTINE ALBINI, MD, PHD[1,2]
SHANNON FOURTNER, MD[1,2]
TERESA QUATTRIN, MD[1,2]

From the [1]Department of Pediatrics, School of Medicine and Biochemical Sciences, University at Buffalo, Buffalo, New York; the [2]Women and Children's Hospital of Buffalo-Kaleida Health, Buffalo, New York; and the [3]Department of Biostatistics, School of Public Health, University at Buffalo, Buffalo, New York.

Corresponding author: Teresa Quattrin, tquattrin@upa.chob.edu.

DOI: 10.2337/dc09-1571

Acknowledgments— The funding and study drug were provided by Immunex/Amgen.

No other potential conflicts of interest relevant to this article were reported.

References

1. Peters MJL. Etanercept treatment in children with new-onset type 1 diabetes: pilot randomized, placebo-controlled, double-blind study (Letter). Diabetes Care 2009; 32:e153. DOI: 10.2337/dc09-1372
2. Mastrandrea L, Yu J, Behrens T, Buchlis J, Albini C, Fourtner S, Quattrin T. Etanercept treatment in children with new-onset type 1 diabetes: pilot randomized, placebo-controlled, double-blind study. Diabetes Care 2009;32:1244–1249
3. Sabbah E, Savola K, Kulmala P, Veijola R, Vähäsalo P, Karjalainen J, Akerblom HK, Knip M. Diabetes-associated autoantibodies in relation to clinical characteristics and natural course in children with newly diagnosed type 1 diabetes: the Childhood Diabetes In Finland Study Group. J Clin Endocrinol Metab 1999;84:1534–1539
4. van Eijk IC, Peters MJ, Nurmohamed MT, van Deutekom AW, Dijkmans BA, Simsek S. Decrease of fructosamine levels during treatment with adalimumab in patients with both diabetes and rheumatoid arthritis. Eur J Endocrinol 2007;156:291–293
5. Lee LF, Xu B, Michie SA, Beilhack GF, Warganich T, Turley S, McDevitt HO. The role of TNF-alpha in the pathogenesis of type 1 diabetes in the nonobese diabetic mouse: analysis of dendritic cell maturation. Proc Natl Acad Sci U S A 2005;102:15995–16000