More on Intralymphatic Injection of Autoantigen in Type 1 Diabetes

TO THE EDITOR: Ludvigsson et al. (Feb. 16 issue)[1] report the results of the DIAGNODE-1 (GAD-Alum [Diamyd] Administered into Lymph Nodes in Combination with Vitamin D in Type 1 Diabetes) trial. They found that injection of alum-formulated glutamic acid decarboxylase (GAD-alum) into the inguinal lymph node plus administration of oral vitamin D was "associated with preservation of residual beta-cell function" and changes to immunologic markers in patients with type 1 diabetes. Although the authors introduce an interesting new approach, their data, as presented, do not support their conclusions adequately.

In brief, the authors do not provide statistical data to support assertions regarding the stable C-peptide level in the patients. They also do not provide raw data to support their accounts of changes in immunologic markers, and they do not adequately discuss how the "historical age-matched patients" from specific trials[2-4] were chosen as a comparison group. Finally, they do not show the standard-error bars that are necessary to understand this small descriptive data set (see Fig. 1 of their article, available at NEJM.org). Conclusive statements based on the results of small pilot studies are inherently tenuous, but they are particularly problematic when inadequate information is provided to support the findings.

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No potential conflict of interest relevant to this letter was reported.

1. Ludvigsson J, Wahlberg J, Casas R. Intralymphatic injection of autoantigen in type 1 diabetes. N Engl J Med 2017;376:697-9.
2. Wherrett DK, Bundy B, Becker DJ, et al. Antigen-based therapy with glutamic acid decarboxylase (GAD) vaccine in patients with recent-onset type 1 diabetes: a randomised double-blind trial. Lancet 2011;378:319-27.
3. Bizzarri C, Pitocco D, Napoli N, et al. No protective effect of calcitriol on beta-cell function in recent-onset type 1 diabetes: the IMDIAB XIII trial. Diabetes Care 2010;33:1962-3.
4. Herold KC, Gitelman SE, Masharani U, et al. A single course of anti-CD3 monoclonal antibody hOKT3gamma1(Ala-Ala) results in improvement in C-peptide responses and clinical parameters for at least 2 years after onset of type 1 diabetes. Diabetes 2005;54:1763-9.

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THE AUTHORS AND A COLLEAGUE REPLY: Several years may be required to conduct well-powered, randomized, placebo-controlled trials with long follow-up in patients with type 1 diabetes. Thus, although conclusive statements based on pilot studies are inherently tenuous, small pilot trials, even without controls, can speed up the process and are needed to test new approaches before the initiation of full-scale, randomized, controlled trials.

In this early trial, autoantigen was injected into each patient's lymph nodes after ethics approval and written informed consent were obtained. There are data from only six patients, and standard errors are now shown in the corrected Figure 1; inherently, such data do not have strong statistical power. In addition, the placebo group in our original Figure 1D should have been labeled as the TrialNet[1] placebo group, not the DIAGNODE-1 placebo group. This error has been corrected.

Our open-label trial had no controls, but when we compare the results regarding C-peptide levels with data from other trials[2,3] and with a control group from a GAD-alum trial in which autoantigen was administered subcutaneously in patients of a similar age,[1] the results appear to be promising (Fig. 1D). Additional data in Figure 1E show in vitro type 2 helper T-cell cytokine secretion that is more pronounced than that observed after subcutaneous administration of higher doses of GAD-alum.[4] Furthermore, although most cytokine levels decreased to very

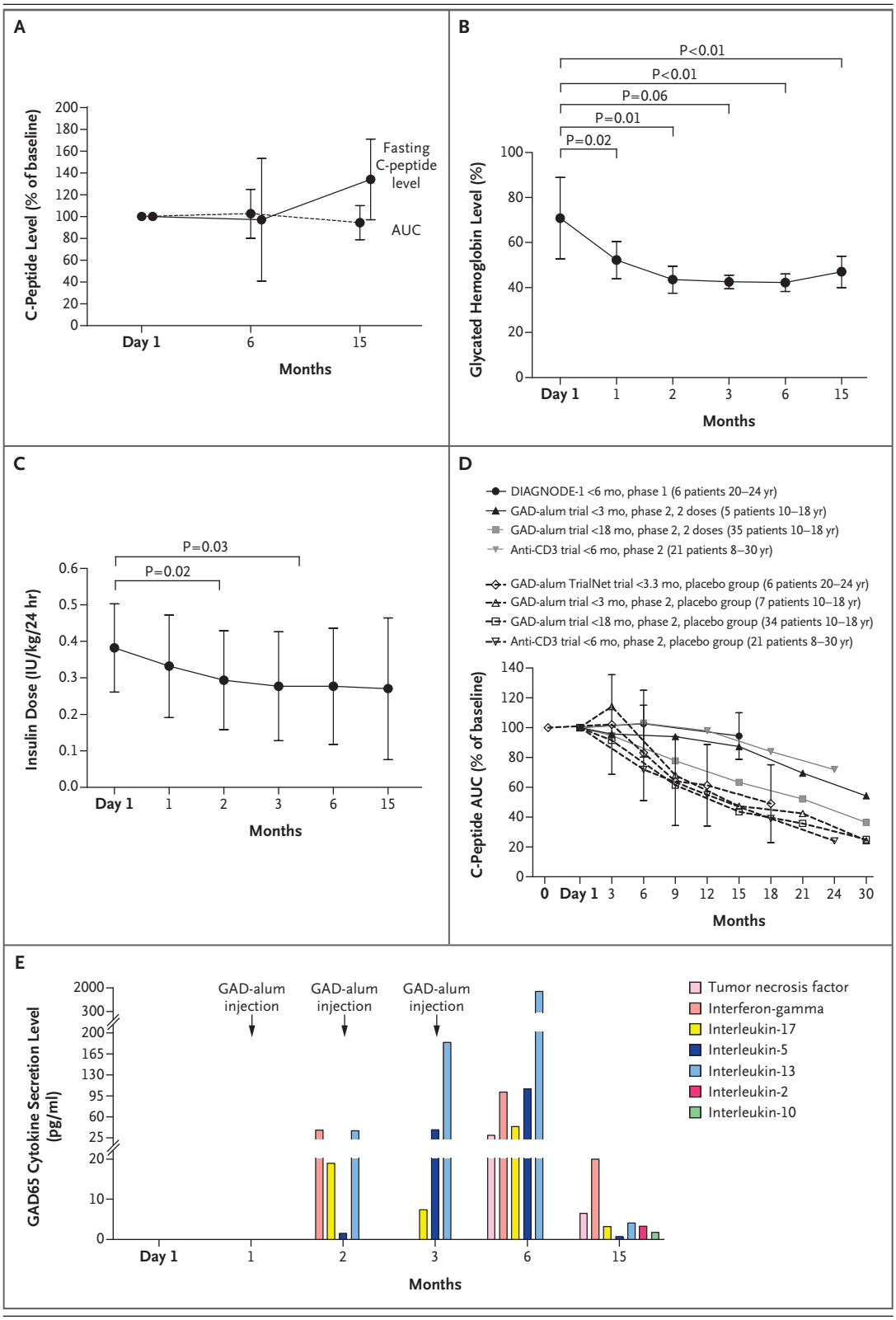

Figure 1 (facing page). Changes in Insulin Doses and C-Peptide, Glycated Hemoglobin, and Cytokine Levels over Time.

Panel A shows fasting C-peptide levels and the mean area under the curve (AUC) of the serum C-peptide level in the six patients after a mixed-meal tolerance test. Panel B shows that the glycated hemoglobin level decreased with time. Panel C shows that the insulin requirement decreased with time. Panel D shows the normalized C-peptide AUC in patients in the DIAGNODE-1 trial as compared with some similar populations of patients in other studies who had received placebo or active immune intervention with subcutaneous GAD-alum (alum-formulated glutamic acid decarboxylase [GAD65]) or anti-CD3 monoclonal antibodies. I bars denote standard errors. Panel E shows the mean levels of GAD-induced cytokine secretion in supernatants from peripheral-blood mononuclear cells from baseline to 15 months.

low levels at 15 months, levels of interleukin-10 and interleukin-2 increased.

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Dr. Tavira reports no potential conflict of interest relevant to this letter. Since publication of their letter, the authors report no further potential conflict of interest.

1. Wherrett DK, Bundy B, Becker DJ, et al. Antigen-based therapy with glutamic acid decarboxylase (GAD) vaccine in patients with recent-onset type 1 diabetes: a randomised double-blind trial. Lancet 2011;378:319-27.
2. Herold KC, Gitelman SE, Masharani U, et al. A single course of anti-CD3 monoclonal antibody hOKT3gamma1(Ala-Ala) results in improvement in C-peptide responses and clinical parameters for at least 2 years after onset of type 1 diabetes. Diabetes 2005;54:1763-9.
3. Ludvigsson J, Faresjö M, Hjorth M, et al. GAD treatment and insulin secretion in recent-onset type 1 diabetes. N Engl J Med 2008;359:1909-20.
4. Axelsson S, Chéramy M, Akerman L, Pihl M, Ludvigsson J, Casas R. Cellular and humoral immune responses in type 1 diabetic patients participating in a phase III GAD-alum intervention trial. Diabetes Care 2013;36:3418-24.

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CORRECTION

Intralymphatic Injection of Autoantigen in Type 1 Diabetes (February 16, 2017;376:697-9). In the lower portion of Figure 1D (page 698), "DIAGNODE-1" should have been "TrialNet." The article is correct at NEJM.org.

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