COMMENT ON TRINH ET AL.

Successful Treatment of Immune Checkpoint Inhibitor–Induced Diabetes With Infliximab. Diabetes Care 2019;42:e153–e154

Anna Galligan, Balasubramanian Krishnamurthy, and Thomas W. Kay

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Trinh et al. (1) have described normalization of plasma glucose concentrations coinciding with administration of the tumor necrosis factor (TNF)-α inhibitor infliximab in a patient who had developed diabetes after treatment with immune checkpoint inhibitors (CPI).

Diabetes associated with programmed cell death (PD)-1/PD-ligand 1 inhibition is a significant complication occurring in around 0.9% of patients. The classic presentation is acute rise in blood glucose concentration with relatively low HbA_{1c} and steroid-unresponsive progression to permanent islet failure. In a cohort of 64 patients, C-peptide was suppressed in more than 90% and GAD autoantibody was present in approximately half; 62% expressed the high-risk class II HLA allele, HLA-DR4 (2).

The case reported by Trinh et al. is atypical. Presentation was late and occurred after intra-articular steroid injections (known to cause systemic side effects such as diabetes). An anti-islet cell IgG titer was 1:100 at baseline, presumably measured by the now-superseded indirect immunofluorescence assay. HLA and autoantibodies to GAD, IA-2, and zinc transporter 8 were not reported, meaning there was no other evidence for islet autoimmunity. Baseline insulin and C-peptide responses to a mixed-meal tolerance test were increased suggesting peripheral insulin resistance, as might be observed with steroid-induced diabetes. It is unclear whether the first test was carried out on insulin treatment. Infliximab then coincided with a decrease rather than increase in plasma C-peptide level. These data, as the authors themselves suggest, indicate reversal of insulin resistance rather than reversal of insulin deficiency.

Infliximab and other biologics are routinely used for the treatment of immune-related adverse events such as colitis and arthritis.

In adults with preexisting GAD antibodies, anti-TNF preceded new-onset type 1 diabetes (T1D) and increased antibody titer, suggesting that the drug was unable to prevent progression and may have played a role in promoting autoimmunity (3). In a pilot study of 18 children with newly diagnosed T1D, etanercept resulted in lower HbA_{1c} and insulin requirements (4). A randomized controlled trial in stage 2 ("presymptomatic") T1D using the fully human anti-TNF monoclonal antibody golimumab is in progress (5). Reports of improved insulin sensitivity and hypoglycemia in patients with T1D and type 2 diabetes after anti-TNF presumably reflect upregulation of glucose transporter mechanisms (6). This mechanism may explain the normalization of plasma glucose in the reported patient.

Before this report, there had been no published data regarding the role of immune modulation for CPI-related diabetes, and the most appropriate agent is not known. Similarly, no drugs are licensed for the prevention or reversal of spontaneous T1D.

It is timely to consider the role of immune therapies for CPI-related diabetes, and TNF inhibition may turn out to be useful. However, it is not sufficiently clear that the case reported by Trinh et al. demonstrates reversal of autoimmune diabetes. Therefore, it is not a basis for considering the clinical use of anti-TNF for more typical cases.

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

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St Vincent's Institute of Medical Research, Fitzroy, Australia
Department of Medicine, The University of Melbourne, St Vincent's Hospital, Fitzroy, Australia
Corresponding author: Anna Galligan, agalligan@svi.edu.au