Routine Blood Glucose Monitoring Does Not Predict Onset of Immune Checkpoint Inhibitor–Induced Type 1 Diabetes

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Immune checkpoint inhibitors (ICI) are revolutionizing the treatment of many advanced-stage cancers; however, serious immune-related adverse events can occur including ICI-induced type 1 diabetes (ICI-T1D) (1). There is an increased reporting of ICI-T1D especially after anti–PD-1 or anti–PD-L1 therapy, with an incidence of ∼1–2% (2,3). ICI-T1D presents acutely with significant hyperglycemia, mostly with life-threatening diabetic ketoacidosis, and is most common during the first 3 months after the start of treatment (3). However, blood glucose (BG) values are often normal leading up to initial presentation of ICI-T1D (4). Our previous research showed that a minority of the patients who develop ICI-T1D have type 1 diabetes (T1D)-associated antibodies at diabetes presentation (3); however, there is a much stronger association between ICI-T1D development and HLA-DR4 alleles, which also confers significant genetic risk for prototypical childhood-onset T1D. Approximately one in four advanced melanoma patients with HLA-DR4 will develop ICI-T1D (5). Currently, there are no guidelines on how to screen and monitor patients receiving ICI therapy for T1D development, which could be done by measuring T1D-associated antibodies, HLA typing, or monitoring BG. Therefore, we investigated whether routine monitoring of BG at ICI infusion visits (every 2 weeks) can predict the onset of hyperglycemia associated with ICI-T1D.

At a single center, we retrospectively reviewed random venous BG results of 89 adults (13 developed ICI-T1D, 76 did not) with advanced melanoma (stage III unresectable and stage IV) who received ICI (anti–PD-1 or anti–PD-L1 with or without anti–CTLA-4) prior to and 18 weeks after the start of ICI treatment. Patients were diagnosed with T1D based on BG values, hemoglobin A_{1c}, requirement for permanent insulin treatment, and C-peptide values after review of inpatient, outpatient, and emergency department visit notes and laboratories. BG values (means ± SD) were compared at all time points between ICI-T1D and non-T1D groups with a Mann-Whitney *U* test. The Colorado Multiple Institutional Review Board approved this study. Mean age was 53.2 ± 12.1 and 54.1 ± 16.8 years and 24% and 32% were female in the T1D group and in the non-T1D group, respectively. Before ICI treatment, BG was 102.5 ± 20.6 mg/dL (5.7 ± 1.1 mmol/L) and 98.6 ± 11.3 mg/dL (5.5 ± 0.6 mmol/L) in the T1D group and non-T1D group (P = ns). As depicted in Fig. 1, BG remained normal in the non-T1D group (103.3 ± 24.3 mg/dL) (5.7 ± 1.4 mmol/L); in the T1D group, last measured BG before diabetes onset (2 weeks prior) was 119.5 ± 12.6 mg/dL (6.6 ± 0.7 mmol/L) and BG at T1D onset was 381.5 ± 149.5 mg/dL (21.2 ± 8.3 mmol/L) ($P < 0.001$ for both in comparisons with non-T1D).

Of 13 patients who developed ICI-T1D, 7 (54%) presented with diabetic ketoacidosis that required hospital admission. ICI-T1D developed (in 50% after anti–PD-1 and 50% after anti–PD-1/CTLA-4 combination) at variable intervals during the 18 weeks of treatment (range 2–18), and 77% (10 of 13) of the case subjects developed T1D within the first 90 days after the start of ICI treatment. We were also able to evaluate seven pre- and six post-treatment serum for T1D-associated antibodies (those directed against insulin, GAD, islet antigen 2, and zinc transporter 8) using radiobinding assays. Only one of seven (14%) had T1D-associated antibodies from pretreatment serum and that was a single antibody directed to GAD, while four of six had antibodies at or after ICI-T1D onset. One patient had two antibodies directed to GAD and insulin, while three others only had single insulin antibodies. As these patients were taking exogenous insulin, this indicates that it is possible to make insulin antibodies after ICI treatment. Seven of 10 (70%) ICI-T1D patients had HLA-DR4.

ICI-T1D presents with a very rapid onset of hyperglycemia and, in the majority of cases, diabetic ketoacidosis (3). At presentation, hemoglobin A_{1c} levels are mildly-to-moderately elevated and C-peptide levels are very low or absent (3). This study confirmed our previous research that >70% of patients develop ICI-T1D in the first 90 days after the first dose (3). The strengths of our study include *1*) a large longitudinal data set of BG with comparison of two groups (ICI-T1D and ICI with no T1D) having the same cancer and *2*) the

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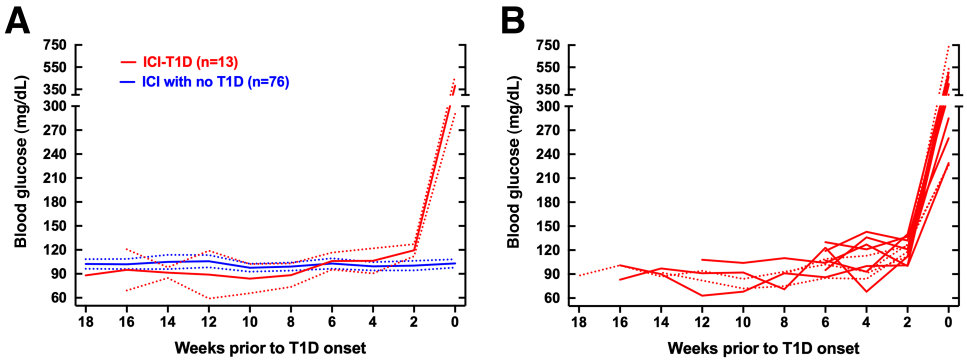

Figure 1—Longitudinal BG values from advanced stage melanoma patients receiving ICI therapy. *A*: Changes in longitudinal BG values measured every 2 weeks in those who developed ICI-T1D (n = 13) and those who received ICI and did not develop T1D (n = 76); shown are means and 95% CIs. *B*: Individual BG values for the ICI-T1D individuals over time. Dotted line indicates glucocorticoid use prior to ICI-T1D onset (n = 4).

paucity of T1D-associated antibodies from pre-/posttreatment serum and HLA alleles for a subset of ICI-T1D patients. Our study is not without limitations, which include retrospective data collection of BG values and variable exposure to glucocorticoids, as some patients (ICI-T1D and ICI without T1D) used steroids temporarily at various times for other immune-related adverse events related to ICI treatment. Four patients in the ICI-T1D group received glucocorticoids prior to T1D onset; however, glucocorticoid-induced hyperglycemia is unlikely, as all 13 ICI-T1D patients required permanent exogenous insulin treatment and many had low/undetectable C-peptide levels.

Taken together, our results indicate that routine monitoring of BG at ICI infusion visits does not predict the rapid onset of hyperglycemia associated with ICI-T1D. There is a need to monitor BG levels more vigilantly for patients at high risk, such as those having HLA-DR4. We speculate that use of continuous glucose monitoring or daily self-monitoring of BG may be helpful for earlier diagnosis of dysglycemia in patients receiving these state-of-the-art therapies who develop ICI-T1D.

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