Reporting of Immune Checkpoint Inhibitor Therapy–Associated Diabetes, 2015–2019

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Immune checkpoint inhibitors (ICIs), including cytotoxic T cell–associated protein-4 (CTLA-4) inhibitors, programmed cell death protein-1 (PD-1) inhibitors, and programmed death-ligand 1 (PD-L1) inhibitors, have greatly improved the clinical outcomes of cancer patients (1). However, immune-related adverse effects involving various organs, including endocrine organs, can occur during ICI therapy (2). Cases of diabetes associated with ICI therapy have also been reported, which can be life-threatening (3–5). However, the incidence and characteristics of ICI-associated diabetes mellitus (ICI-DM) remain unclear. Therefore, we conducted a retrospective study with data from the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), a pharmacovigilance database, to investigate this issue (6).

We used the FAERS to identify all reported cases of new-onset diabetes that were associated with ICIs approved by the FDA (i.e., ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, and cemiplimab) between 1 January 2015 and 31 December 2019. Patients with new-onset type 1 diabetes, fulminant type 1 diabetes, diabetic ketoacidosis (DKA), or diabetic ketosis secondary to ICI therapy were considered to have ICI-DM. Those with DKA or diabetic ketosis secondary to type 2 diabetes or diabetes without detailed subtypes were excluded. We then used the χ^2 test to compare the proportion of ICI-DM cases with all ICI-associated adverse events by year, sex, age, and treatment regimens. We also used a logistic regression analysis to assess the association between therapy and risk of ICI-DM. Ethics review and informed consent were waived in this study because all the analyzed data sets are deidentified and publicly available.

We identified 735 cases of ICI-DM in total; 415 case subjects were male. The median age of patients with ICI-DM was 66 years (range 15–95). Melanoma and lung cancer were the most common cancer types among these patients (Table 1). Among the 735 case subjects with ICI-DM, 183 (24.90%) had fulminant type 1 diabetes and 338 (45.99%) presented in DKA or diabetic ketosis. Of cases of ICI-DM, 183 (24.90%) had severe outcomes (life-threatening or death) and 41 (5.58%) resulted in deaths.

Overall, the incidence of ICI-DM was ~1.27% (735 of 57,683). An obvious and consistent increase in reporting of ICI-DM over time was observed: from 17 in 2015 to 331 in 2019 (Table 1). The proportion of cases of ICI-DM to all reported adverse events associated with ICIs also significantly increased over time, from 0.67% (88 of 13,070) in 2015–2016 to 0.96% (117 of 12,251) in 2017, 1.39% (199 of 14,271) in 2018, and 1.83% (331 of 18,091) in 2019 ($\chi^2 = 93.44$, $P < 0.0001$, Bonferroni corrected). Significant differences were observed in the incidence of ICI-DM by therapy (combination therapy of anti–CTLA-4/anti–PD-1/anti–PD-L1 219 [2.60%] of 8,415 vs. anti–PD-1 therapy 466 [1.18%] of 39,735 vs. anti–PD-L1 therapy 34 [0.73%] of 4,658 vs. anti–CTLA-4 therapy 16 [0.33%] of 4,875; $\chi^2 = 166.92$, $P < 0.0001$, Bonferroni corrected). Patients who received combination therapy of anti–CTLA-4/anti–PD-1/anti–PD-L1 tended to have higher risk of ICI-DM compared with those on other regimens of ICIs, with adjustment for age, sex, cancer type, and reporting year (odds ratio 1.46, 95% CI 1.22–1.74). No significant differences were observed in incidence by sex (male 415 [1.31%] of 31,359 vs. female 262 [1.44%] of 18,143; $\chi^2 = 1.24$, $P = 0.27$), age (<65 years 284 [1.84%] of 15,452 vs. ≥65 years 333 [1.72%] of 19,332; $\chi^2 = 0.66$, $P = 0.42$).

To our knowledge, this is the first study to report the incidence of ICI-DM and the

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Table 1—Characteristics of patients with ICI therapy–associated diabetes

Characteristics	Patients	Severe outcomes
All	735 (100)	183 (100)
Sex		
Male	415 (56.46)	107 (58.47)
Female	262 (35.65)	69 (37.70)
Not specified	58 (7.89)	7 (3.83)
Age (years)		
<65	284 (38.64)	79 (43.17)
≥65	333 (45.31)	93 (50.82)
Not specified	118 (16.05)	11 (6.01)
Cancer types		
Melanoma	248 (33.74)	57 (31.14)
Lung	191 (25.99)	62 (33.88)
Renal	91 (12.38)	21 (11.48)
Others	205 (27.89)	43 (23.50)
Reporting year*		
2015	17 (2.31)	9 (4.92)
2016	71 (9.66)	20 (10.93)
2017	117 (15.92)	27 (14.75)
2018	199 (27.07)	54 (29.51)
2019	331 (45.04)	73 (39.89)
Treatment regimens		
Anti–PD-1 therapy	466 (64.40)	127 (69.40)
Anti–PD-L1 therapy	34 (4.63)	6 (3.28)
Anti–CTLA-4 therapy	16 (2.18)	2 (1.09)
Combination therapy of anti–CTLA-4/anti–PD-1/anti–PD-L1	219 (29.79)	48 (26.23)

Data are *n* (%). *Reporting year refers to the year of "latest FDA received date" in the FAERS.

relevant clinical outcomes with a large sample size. Our analysis indicated that there was a substantial increase in reporting the incidence of ICI-DM over time. We found that ~25% of patients with diabetes secondary to ICI therapy had severe outcomes that were either life-threatening or fatal. As ICI therapy has been increasingly applied in cancer patients, it is essential to remind clinicians that ICI-DM is also a potentially life-threatening adverse event of ICI therapy. Therefore, it is suggested that glucose levels be regularly monitored during ICI therapy for cancer patients, especially for patients who received combination therapy of ICIs. In our present study, we were unable to capture all comorbidities and all concomitant therapies in patients with ICI-DM due to data restrictions, but few were reported as receiving concurrent diabetes medications. In addition, other potentially useful clinical data like clinical course, autoantibodies associated with type 1 diabetes, C-peptide, and HLA-DR4 haplotype status could not be included in our present analysis unfortunately. Further studies are needed to confirm our findings and identify the mechanisms and predictors of ICI-DM.

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Author Contributions. J.L., H.Z., and L.Z. were responsible for the conception and design of the study. J.L. acquired the data from the FAERS database. J.L., H.Z., and Y.Z. were responsible for data analysis, interpretation of data, and drafting and writing of the manuscript. W.F., Y.Y., and Y.H. contributed to the discussion and revision of the intellectual content. All authors participated in final approval of the article and agreed to be accountable for all aspects of the work. L.Z. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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