Increased Reporting of Immune Checkpoint Inhibitor–Associated Diabetes

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Immune checkpoint inhibitors (CPI) have proven remarkably effective in treating many types of malignancies but have been associated with significant risk for immune-related adverse events (irAEs) (1). Among these, new onset of insulin-dependent diabetes mellitus (DM) occurs in 0.2–1.0% of patients (2,3) and is being seen more frequently as CPI become more widely used. However, the incidence, clinical course, and pathogenesis of CPI-associated DM (CPI-DM) are not well understood.

To better understand the characteristics of CPI-DM, we analyzed VigiBase (4), the World Health Organization's database of individual case safety reports, and detected 283 cases of new-onset DM from 2014 to April 2018 following treatment with CPI using the following preferred terms according to MedDRA (Medical Dictionary for Regulatory Activities): diabetic ketoacidosis (DKA), diabetic ketosis, type 1 diabetes mellitus, or fulminant type 1 diabetes mellitus; any one of these was sufficient to define CPI-DM. We noted a marked increase in reporting of CPI-DM over this time period, with over 50% of cases reported in 2017 (Table 1). Overall, half of the patients with DM presented in DKA (50.2%); 5.6% of all cases were also on steroids at diagnosis of DM, and 6.4% were on noninsulin diabetes medications in addition to insulin. Prior and/or subsequent cancer therapies are unknown, but no other immunomodulatory medications were reported.

Onset of DM ranged from 5 to 790 days after the first dose of CPI (median 116 days, interquartile range [IQR] 58–207.5, $n = 91$). Of the 54 patients for whom timing of CPI and DM onset is available, 69% developed DM while on CPI or within 1 month after cessation, 22% developed DM between 1 and 3 months later, and 9% developed DM more than 3 months after stopping CPI; maximum duration from cessation of CPI to DM onset was 247 days. CPI-DM was associated with at least one other irAE in 21% of cases and with another endocrine irAE in 8.5% of cases (thyroid, pituitary, or adrenal) (Table 1).

In those who developed DM, there was a wide variability in duration of CPI, ranging from 1 to 24 doses (median 3 doses, IQR 1–7, $n = 48$). The majority of cases of CPI-DM occurred in individuals treated with anti–programmed cell death 1 (anti-PD-1) monotherapy (52.7% nivolumab, 23.3% pembrolizumab), with only a small fraction having been treated with anti–programmed death-ligand 1 (anti-PD-L1) monotherapy (1.4% each for atezolizumab and durvalumab, no cases with avelumab). Seventeen percent of CPI-DM cases were treated with dual therapy, with either anti-PD-1 or anti-PD-L1 plus anti–cytotoxic T-lymphocyte–associated protein 4 (anti-CTLA4, ipilimumab; no cases reported with tremelimumab). Twelve cases of CPI-DM were found among patients treated with ipilimumab monotherapy. None of these 12 patients were previously treated with antihyperglycemic medications. They were mostly from the Americas (50%) and Europe (42%), with one case from Australia. Future characterization of cases of ipilimumab-associated DM will be important, as the only previously reported case of anti-CTLA4–associated diabetes was from Japan (5),

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Table 1—Patients with immune CPI-associated DM (median age 64 years, IQR 56–72; 56% male)

	Percentage
Region	
Americas	45.2
Europe	26.2
Asia	25.1
Oceania	3.5
Immune CPI regimen	
All patients	100.0
Anti-PD-1 monotherapy	
Nivolumab	52.7
Pembrolizumab	23.3
Anti-PD-L1 monotherapy	
Atezolizumab	1.4
Durvalumab	1.4
Anti-CTLA4 monotherapy (ipilimumab)	4.2
Combination anti-PD-1/PD-L1 + anti-CTLA4	17.0
Primary cancer (n = 238)	
Melanoma	43.3
Lung	32.3
Renal	10.1
Other	14.3
Year reported, % of all patients (% listed in DKA)	
2014	1.1 (66.7)
2015	9.2 (76.9)
2016	23.3 (57.6)
2017	52.3 (40.5)
2018 (through 1 April)	14.1 (55.0)
Associated AEs	
Any irAE	20.8
Endocrine	8.5
Thyroid dysfunction	7.1
Adrenal insufficiency	2.1
Hypophysitis/hypopituitarism	2.5
Other	
Colitis	3.9
Pancreatitis	3.5
Dermatitis/rash	3.2
Hematologic involvement	2.1
Hepatic involvement	2.1
Arthralgia, pneumonitis, encephalitis, or myocarditis	4.3
Death	2.8

n = 283 except where stated otherwise.

where autoimmune DM features and HLA background differ from much of the world. In all patients who received anti-CTLA4, whether in combination or as monotherapy, DM developed within 75 days of the first dose of ipilimumab.

These data are limited by the lack of reported frequency of CPI use, thus making it difficult to determine the drug-specific and overall incidence of CPI-DM, and by the lack of other potentially useful data including clinical course, ethnicity, C-peptide, autoantibody status, and other risk factors. Furthermore, our inability to identify relatively mild forms of DM, e.g., patients who were hyperglycemic but did not have DKA, may lead to an overestimation of the rapidity of disease progression or the percentage of patients that present in DKA. Our chosen search terms also may have missed CPI-DM reported using other less-specific terms.

In summary, this case series represents the largest description of CPI-DM to date. These data indicate that there is an increased reporting of rapidly progressive CPI-DM, with patients frequently presenting in DKA. The frequency and mechanism of CPI-DM are unknown. We report the first possible association of ipilimumab monotherapy with DM outside of Japan (5), though the significance and nature of this association are unclear. An improved understanding and awareness of CPI-DM should lead to improved detection and treatment of diabetes. Specific information regarding patients who developed CPI-DM, review of pancreatic histology in CPI-DM patients, and targeted genetic analysis of CPI-DM patients are avenues of research that will be useful to efforts to understand this novel form of diabetes.

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References

1. Tocut M, Brenner R, Zandman-Goddard G. Autoimmune phenomena and disease in cancer patients treated with immune checkpoint inhibitors. Autoimmun Rev 2018;17:610–616

2. Stamatouli AM, Quandt Z, Perdigoto AL, et al. Collateral damage: insulin-dependent diabetes induced with checkpoint inhibitors. Diabetes 2018;67:1471–1480

3. Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. JAMA Oncol 2018;4:173–182

4. Lindquist M. VigiBase, the WHO global ICSR database system: basic facts. Ther Innov Regul Sci 2008;42:409–419

5. Yamazaki N, Kiyohara Y, Uhara H, et al. Phase II study of ipilimumab monotherapy in Japanese patients with advanced melanoma. Cancer Chemother Pharmacol 2015;76:997–1004