Systematic Review or Meta-analysis

Immune checkpoint inhibitor-induced Type 1 diabetes: a systematic review and meta-analysis

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Aim To conduct a systematic review and meta-analysis to understand the timing and factors associated with anti-programmed cell death protein-1 (PD-1)/anti-programmed cell death protein-1 ligand (PD-L1) inhibitor-induced Type 1 diabetes.

Methods   We searched MEDLINE, EMBASE, SCOPUS and Cochrane databases (August 2000–2018) for studies of any design on immune checkpoint inhibitors. A total of 71 cases were reviewed from 56 publications. Comparisons were made using Fisher's exact and Student's t-tests.

Results   The mean ± SD age at Type 1 diabetes presentation was 61.7±12.2 years, 55% of cases were in men, and melanoma (53.5%) was the most frequent cancer. The median time to Type 1 diabetes onset was 49 (5–448) days with ketoacidosis in 76% of cases. The average ± SD HbA_{1c} concentration was 62 ± 0.3 mmol/mol (7.84±1.0%) at presentation. All cases had insulin deficiency and required permanent exogenous insulin treatment. Half of the cases had Type 1 diabetes-associated antibodies at presentation, and those with antibodies had a more rapid onset (P=0.005) and higher incidence of diabetic ketoacidosis (P=0.02) compared to people without antibodies.

Conclusions   Many people developed Type 1 diabetes within 3 months of initial PD-1/PD-L1 inhibitor exposure. People presenting with Type 1 diabetes-associated antibodies had a more rapid onset and higher incidence of ketoacidosis than those without antibodies. Healthcare providers caring for people receiving these state-of-the-art therapies need to be aware of this potential severe adverse event.

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Introduction

Immunotherapy with drugs that block immune checkpoints has emerged as a beneficial treatment for advanced stage cancers. Immune checkpoints include cytotoxic T-lymphocyte antigen 4 (CTLA-4) and its receptors CD80/86, along with programmed cell death protein 1 (PD-1) and its ligand (PD-L1) [1–5]. CTLA-4 and PD-1 are expressed on the surface of activated T lymphocytes and engage their receptors on antigen-presenting cells and various tumours [6]. Upon activation, lymphocytes are rendered unresponsive. Immune checkpoint blockade inhibits negative immune regulation, allowing an immune response directed towards cancer cells.

Monoclonal antibodies directed against CTLA-4, PD-1 and PD-L1 are used in the treatment of many advanced cancers, including melanoma, lung cancer, renal cancer, head and neck cancers, urothelial cancers and others [1]. The clinically approved CTLA-4 inhibitor is ipilimumab, while current PD-1 inhibitors are nivolumab and pembrolizumab, and PD-L1 inhibitors include atezolizumab, avelumab and durvalumab. Inhibition of immune checkpoints can also cause immune-related side effects, especially autoimmunity directed towards self-tissues [7]. One such side effect is Type 1 diabetes, which is rare but can present with life-threatening diabetic ketoacidosis and is predominantly linked to anti-PD-1/PD-L1 therapies [8–12]. Type 1 diabetes is now listed as a treatment-related adverse reaction in the prescribing labels for nivolumab, pembrolizumab, avelumab and durvalumab [13–16].

The factors associated with PD-1/PD-L1 inhibitor-induced Type 1 diabetes are not well defined as the incidence is estimated at ~1% from case series at large academic medical centres (27/2960, 0.9%) [17] and the prescribing label of

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What's new?

- This systematic review showed that the majority of people developed immune checkpoint inhibitor-induced Type 1 diabetes within 3 months of initial treatment.

- People presenting with Type 1 diabetes-associated antibodies had a more rapid onset and higher incidence of diabetic ketoacidosis at presentation.

- Healthcare providers caring for people receiving these state-of-the-art therapies need to be aware of this potential life-threatening adverse event.

nivolumab reporting 17/1994 (0.9%) [15]. This represents a limited number of new-onset Type 1 diabetes cases following anti-PD-1/PD-L1 therapy; however, the events are clinically significant. To prevent significant morbidity and mortality related to diabetic ketoacidosis in people with advanced cancers, an understanding of the clinical and laboratory measurements surrounding this immune-related adverse event from a larger number of cases is needed. We conducted a systematic review of published cases and case series of new-onset PD-1/PD-L1 inhibitor-induced Type 1 diabetes to analyse time to diabetes onset, presentation with diabetic ketoacidosis, Type 1 diabetes-associated antibodies and other metabolic measurements.

Methods

Data sources and searches

A systematic review and meta-analysis was conducted to answer the clinical question: what are the timing and factors associated with diabetes onset after treatment with immune checkpoint inhibitors? A comprehensive search of databases (Medline In-Process and Other Non-Indexed Citations, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus) for papers published from 1 August 2000 to 14 August 2018, in English, was conducted based on the terms 'diabetes' and 'immune checkpoint inhibitors' (Table S1). References in the case reports and series were manually reviewed for additional cases. We contacted one author for missing information (agents administered to patients) from one case series [10]. A total of 71 cases were identified from a total of 56 publications (see references in Supporting Information). A flow diagram for the study is provided in Fig. 1.

Study selection

Inclusion criteria

We included all published case reports and series that reported new-onset diabetes after PD-1/PD-L1 inhibitor therapy. We used the American Diabetes Association criteria for the

diagnosis of diabetes and diabetic ketoacidosis including grading for severity (severe, moderate and mild) [18,19]. These data included blood glucose, HbA$_{1c}$, and other related laboratory measures. Blood glucose and HbA$_{1c}$ levels before exposure to PD-1/PD-L1 were used to define new-onset vs existing diabetes. We collected data regarding serum electrolytes to calculate an anion gap, arterial blood gas, and urine/blood ketone positivity to determine the presentation and severity of diabetic ketoacidosis (Table S2). C-peptide levels were documented as absent or inappropriately low for the concomitant blood glucose. Amylase and lipase levels were extracted to determine exocrine pancreas involvement. Type 1 diabetes-associated antibodies were considered positive if an individual was reported as being positive for these antibodies. All cases reported antibodies measured against glutamic acid decarboxylase (GAD) but not all cases reported results for other antibodies, such as islet cell antibodies, insulin, islet antigen 2 and zinc transporter 8. The presence of one human leukocyte antigen (HLA) allele (DR4, DQ8, DR3, DQ2) was considered high-risk for Type 1 diabetes (Table S2).

Exclusion criteria

Case reports/series with people who were previously diagnosed with Type 2 diabetes prior to the start of anti-PD-1 or PD-L1 therapy were excluded.

Data extraction and quality assessment

We used an adapted version of the Newcastle–Ottawa scale, previously used in systematic reviews and meta-analyses of case reports/series [20], to assess the methodological quality of case reports and case series. Using this approach, we assessed the quality of each case report with regard to four domains: selection; ascertainment; causality; and reporting. We used five criteria in the form of questions, with binary answers (yes/no), as to whether the report met these criteria or not. The questions were as follows:

1. Did the person(s) represent the whole case(s) of the medical centre?

2. Was the diagnosis correctly made for new-onset diabetes?

3. Were all important data cited in the report?

4. Were other possible diagnoses excluded?

5. Were factors associated with Type 1 diabetes measured?

Two reviewers assessed the methodological quality of the studies and extracted the relevant data for the published cases based on the inclusion/exclusion criteria (D.K and A.S). A third reviewer analysed the results and made a final decision regarding the quality of reports (H.K.A).

Data synthesis and analysis

Statistical analyses were conducted using STATA version 15 (StataCorp LP, College Station, TX, USA). Binary variables
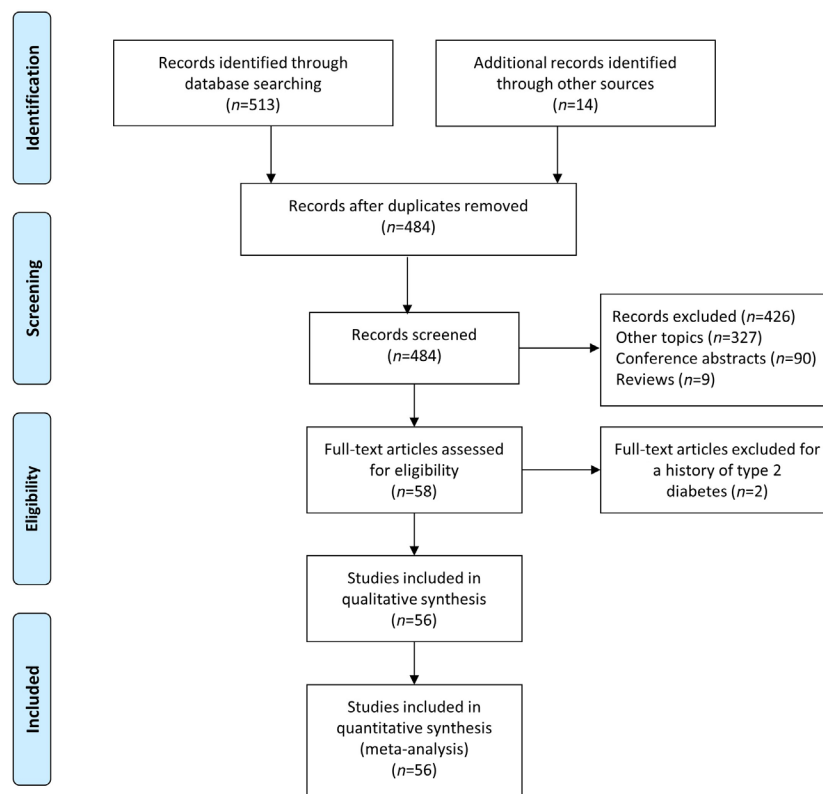
FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of the study. A total of 56 publications were selected, which resulted in 71 cases of new-onset Type 1 diabetes following immune checkpoint blockade.

(diabetic ketoacidosis and the presence of Type 1 diabetes-associated antibodies) were compared using Fisher's exact test. Continuous variables (age, duration of diabetes and HbA_{1c}) were compared using Student's *t*-test. Unadjusted simple linear regression was carried out using GraphPad Prism 8.0 software to compare time to diabetes onset by HbA_{1c}. A two-tailed *P* value of <0.05 was taken to indicate statistical significance.

Results

Cases of new-onset diabetes

We identified 58 publications representing 75 cases from 1 August 2000 to 14 August 2018 (Fig. 1). Four cases in two publications were excluded because of a pre-existing diagnosis of diabetes. A total of 71 cases in 56 publications were included in the review. Fifty-six cases had high, 12 had moderate, and three had low methodological quality (Table S3).

The mean (range) age of individuals identified was 61.7 (23–84) years and 55% were men (Table 1). The most common cancer treated was melanoma (53.5%), followed by lung cancer (26.8%). Other cancers comprised <10% of the cases. The most frequently used monoclonal antibodies were those directed towards PD-1 (nivolumab and pembrolizumab) in 90% of cases, while the remaining 10%

received anti-PD-L1 therapies (atezolizumab, avelumab or durvalumab). There was no difference among the agents used in terms of diabetes duration as well as comparing metabolic and immunological features at presentation (Table 1), indicating a potential drug class effect for PD-1 and PD-L1 inhibitors to induce Type 1 diabetes; however, more cases, especially with anti-PD-L1 agents, are needed to confirm this observation.

Clinical and laboratory features

The median duration until diabetes onset after the start of anti-PD1/PD-L1 treatment was 49 days. The earliest time to onset was 5 days and the longest duration was reported at 448 days. Remarkably, 71% of the cases developed new-onset Type 1 diabetes within 3 months after the first exposure to anti-PD-1/PD-L1 treatment (Fig. 2a). When examining the agents individually, the median duration to diabetes was 42 days for pembrolizumab, 73.5 days for nivolumab, and 84 days for the anti-PD-L1 agents (Fig. 2b).

The majority (76%) of the people presented with diabetic ketoacidosis, which is associated with elevated risk of morbidity and mortality based on severity (Table 1). Among the cases with available criteria by which to assess diabetic ketoacidosis severity, 38.9% presented with severe, 20.4% with moderate and 11.1% mild ketoacidosis. Blood glucose

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Table 1 Clinical, metabolic and immunological characteristics of anti-programmed cell death protein-1 or anti-programmed cell death protein-1 ligand inhibitor-induced Type 1 diabetes

	All cases (n=71)	Nivolumab (n=38)	Pembrolizumab (n=26)	anti-PD-L1[*] (n=7)
Age, years				
Mean (SD)	61.7 (12.2)	61.4 (12.8)	61.1 (11.4)	65.7 (10.8)
Median	62.0	62.5	61.0	66.5
Range	23–84	28–83	23–82	50–84
Gender				
Female, %	45.0	50.0	38.5	42.8
Cancer type, % (n)				
Melanoma	53.5 (38)	50.0 (19)	73.0 (19)	0 (0)
Lung	26.8 (19)	34.2 (13)	15.4 (4)	28.5 (2)
Renal cell	5.7 (4)	10.6 (4)	0 (0)	0 (0)
Head and neck	7.0 (5)	2.6 (1)	7.7 (2)	28.5 (2)
Urothelial carcinoma	4.2 (3)	0 (0)	0 (0)	43.0 (3)
Other	2.8 (2)	2.6 (1)	3.9 (1)	0 (0)
Duration to diabetes, days				
Mean (SD)	83.5 (88.5)	98.0 (102.1)	65.9 (72.1)	75.0 (39.7)
Median	49	73.5	42	84
Range	5-448	5-448	14-365	21-126
Diabetic ketoacidosis, % (n)				
Present	76.0 (54)	71.0 (27)	80.7 (21)	85.7 (6)
Severe	38.9 (21)	33.3 (9)	52.4 (11)	16.6 (1)
Moderate	20.4 (11)	22.2 (6)	14.3 (3)	33.3 (2)
Mild	11.1 (6)	3.7 (1)	14.3 (3)	33.3 (2)
Not able to assess	29.6 (16)	40.8 (11)	19.0 (4)	16.6 (1)
Blood glucose, mmol/l				
Mean (SD)	33.4 (11.5)	33.8 (12.1)	34.1 (9.5)	29.4 (13.8)
Median	32.2	31.7	34.2	22.8
Range	13.7–67.3	13.7–67.3	15.0–50.5	18.1–56.4
HbA$_{1c}$, mmol/mol				
Mean (SD)	62 (0.3)	60 (0.3)	64 (0.3)	66 (0.4)
Median	61	56	62	66
Range	40–93	40–88	40–93	46–84
Type 1 diabetes-associated antibodies, % (n)				
Present	50.7 (36)	44.7 (17)	57.7 (15)	57.1 (4)
Absent	49.3 (35)	55.3 (21)	42.3 (11)	42.9 (3)
Type 1 diabetes risk HLA genes[†], % (n)				
Present	38.0 (27)	39.5 (15)	38.5 (10)	28.5 (2)
Absent	7.0 (5)	13.1 (5)	0 (0)	0 (0)
Not Reported	55.0 (39)	47.4 (18)	61.5 (16)	71.5 (5)
Ipilimumab (anti-CTLA-4) use[‡], % (n)				
Present	31.0 (22)	31.5 (12)	38.5 (10)	0 (0)
Absent	69.0 (49)	68.5 (26)	61.5 (16)	100.0 (7)

HLA, human leukocyte antigen; PD-1, programmed cell death protein; PD-L1, programmed cell death protein-1 ligand.
[*]Atezolizumab, avelumab and durvalumab.
[†]HLA-DQ-DR risk genes include DR3, DR4, DQ2, DQ8.
[‡]Prior or concurrent use of ipilimumab with anti-PD-1/PD-L1 treatment.

levels at presentation were elevated, with a mean ± SD (range) of 33.4 ± 11.5 (13.7–67.3) mmol/l [602 ± 207 (246–1211) mg/dl]. Average (range) HbA$_{1c}$, a measure of average blood glucose over the preceding 3 months, was 62 ± 0.3 (40–93) mmol/mol [7.8 ± 1.0 (5.8–10.7)%; Table 1]. Interestingly, there was no correlation between HbA$_{1c}$ and time to new-onset Type 1 diabetes (r^2 = 0.001, P=0.78), potentially indicating a short time period of significantly elevated blood glucose prior to diabetes onset (Fig. 3a).

As expected, residual β-cell function, as measured by C-peptide which is secreted in a 1:1 ratio with insulin, was absent or inappropriately low for given blood glucose in all 55 cases for which levels were reported (Table S2). This insulin deficiency was permanent as all cases required

continued treatment with exogenous insulin, and none of the people were reported to have come off insulin. Lipase and/or amylase were elevated in eight of 17 cases that reported these values, which indicates that pancreas inflammation was present in a subset of people with immune checkpoint inhibitor-induced Type 1 diabetes.

Immunological features

Half of the cases had detectable Type 1 diabetes-associated antibodies at presentation, with antibodies directed towards GAD being the most commonly reported. In contrast, ~90% of the people with prototypical childhood-onset Type 1 diabetes have one or more antibodies at clinical diagnosis
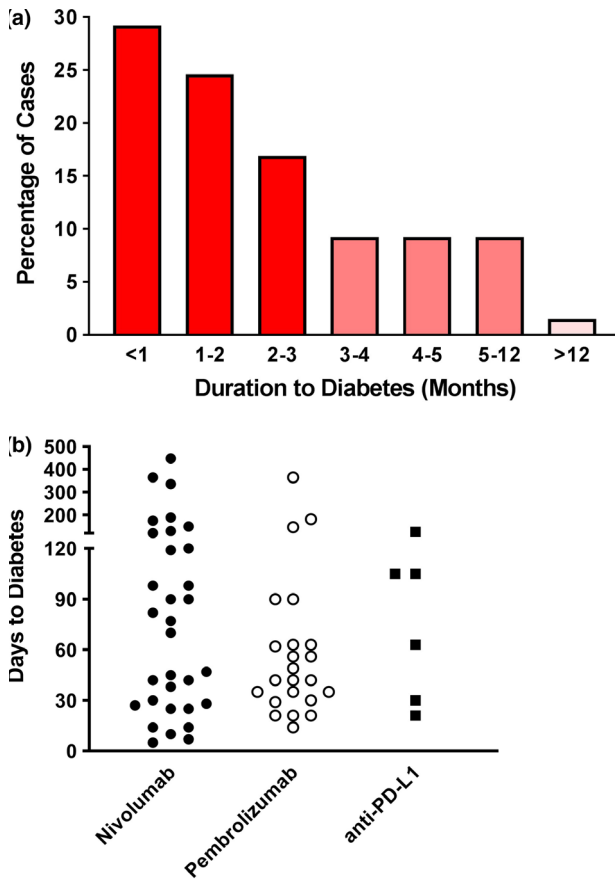
FIGURE 2 Percentage of cases presenting with new-onset Type 1 diabetes stratified by duration from initial anti-programmed cell death protein-1 (PD-1)or anti-programmed cell death protein-1 ligand (PD-L1) exposure. (a) Graph showing that 71% of the cases developed Type 1 diabetes in the first 3 months; *n*=65 cases reporting time to diabetes onset. (b) Duration to diabetes onset by treatment agent.

[21,22]. Cases with positive Type 1 diabetes-associated antibodies had a shorter duration to diabetes onset (55 vs 117 days [95% CI 33.25–76.75 vs 78.03–155.51]; *P*=0.005). Those with antibodies also had a higher incidence of presentation with diabetic ketoacidosis compared to people without traditional Type 1 diabetes-associated antibodies [30/35 (86%) vs 18/30 (60%); *P*=0.02 (Fig. 3b)].

In addition to Type 1 diabetes-associated antibodies, genes within the HLA region are known to predispose significant risk of developing childhood-onset Type 1 diabetes [23]. In particular, the class II DR and DQ genes (e.g. DR4–DQ8 and DR3–DQ2) confer the greatest susceptibility [24,25]. HLA typing was reported in 32 cases, with 27 out of 32 (85%) having at least one Type 1 diabetes risk DR or DQ allele (Table 1). This is comparable to childhood-onset Type 1 diabetes where ~90% of people have at least one of these risk genes [24]. There appears to be a cohort of people with positive Type 1 diabetes-associated antibodies and at-risk HLA that develops diabetes rapidly (Fig. 3C).
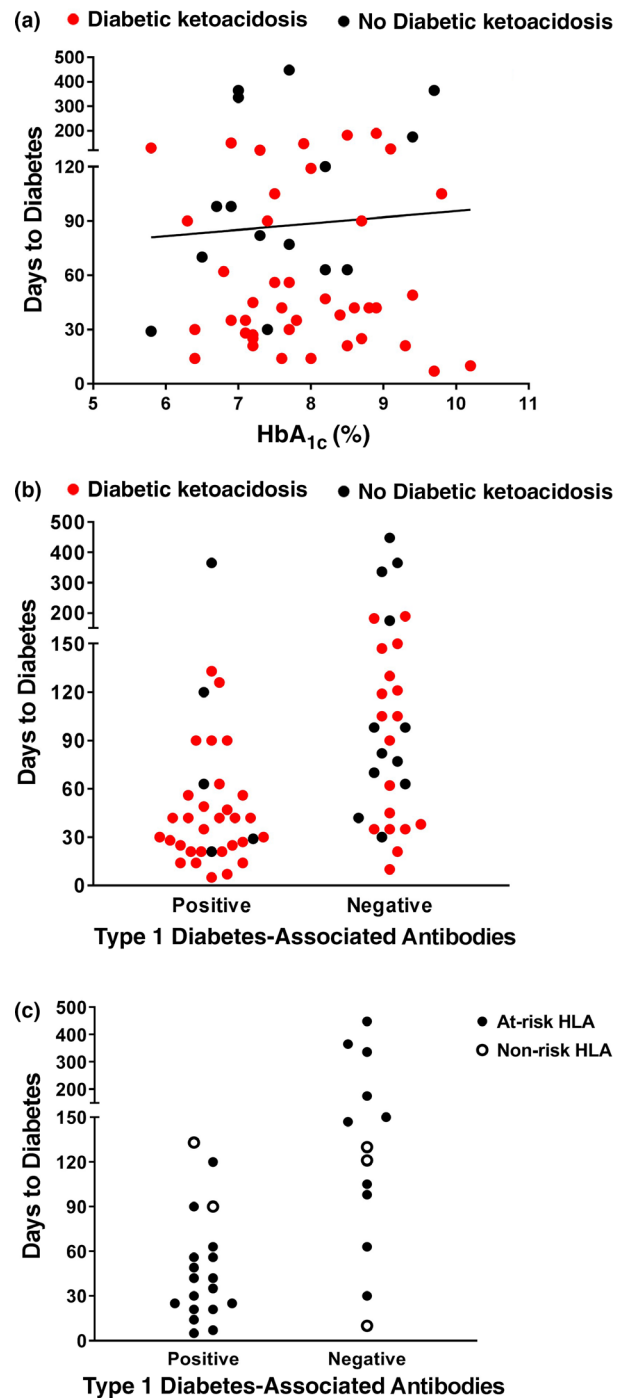

FIGURE 3 Comparison of duration to diabetes onset to HbA$_{1c}$, Type 1 diabetes associated antibodies at presentation, and human leukocyte antigen (HLA) following anti-programmed cell death protein-1 (PD-1) or anti-programmed cell death protein-1 ligand (PD-L1) inhibitor treatment. (a) Duration to Type 1 diabetes onset by HbA$_{1c}$. (b) Duration to diabetes onset by Type 1 diabetes associated antibody positivity. Cases with a shorter duration to diabetes were more likely to present with diabetic ketoacidosis. (c) Duration to Type 1 diabetes onset by antibody positivity and the presence or absence of at-risk HLA genes.

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Prior or concomitant use of another immunotherapy has the potential to increase Type 1 diabetes risk. To investigate this possibility, use of ipilimumab, a CTLA-4 inhibitor which was clinically approved prior to anti-PD-1/PD-L1 therapies, was evaluated in our cases. The use of ipilimumab was reported in only 22 cases (Table 1). There was no association among cases receiving ipilimumab compared to those without for our measured outcomes. Interestingly, none of our reported cases with new-onset Type 1 diabetes following immune checkpoint inhibition occurred with the use of ipilimumab as a single agent.

Discussion

This is the largest and most comprehensive systematic review of case reports and series reporting duration to Type 1 diabetes onset following immune checkpoint inhibitor therapy. As this immune-related adverse event commonly presents with insulin deficiency and life-threatening diabetic ketoacidosis, there is a need to understand the clinical, metabolic and immunological features on presentation. We identified a critical window for disease development within the first 3 months of starting therapy in which 71% of the reviewed cases developed Type 1 diabetes. All of the cases were insulin-deficient at presentation and required permanent treatment with exogenous insulin.

Those people with Type 1 diabetes-associated antibodies, which were predominantly directed against GAD, were more likely to present within a shorter timeframe and with diabetic ketoacidosis compared to those without antibodies at presentation. Slightly more than half of the cases were associated with traditional Type 1 diabetes antibodies, which is similar to a recent case series reporting a rate of 10/25 (40%), along with a faster onset to diabetes with antibodies at presentation [17]. It is unknown whether these antibodies preceded the start of therapy or developed after exposure to immune checkpoint inhibitors. A subset of people may have pre-existing Type 1 diabetes-associated antibodies as disease developed within a few days to weeks after the start of therapy [26]. More research is needed to evaluate all of the traditional Type 1 diabetes-associated antibodies and those directed against post-translationally modified β-cell proteins. Future research also needs to evaluate HLA genes and other potential genetic risk factors, as a limited number of people have had HLA typing performed to date.

The incidence of immune checkpoint inhibitor-induced Type 1 diabetes is estimated at 1% [13–17]. With this frequency, prospective clinical trials assessing PD-1/PD-L1 inhibitor-induced Type 1 diabetes will be challenging, therefore, there is a need to form registries and rigorously review cases reported in the literature. There is evidence from the WHO database of individual case safety reports (VigiBase) that indicates an increased reporting of immune checkpoint inhibitor-associated diabetes [27]. This could be attributable to the increased use of anti-PD-1 and anti-PD-L1

therapies across cancers or differences in patient populations between clinical trials and those treated in clinical practice. Notably, most phase II and III clinical trials excluded people with an existing autoimmune disorder [26].

The majority of cases developing Type 1 diabetes were treated for melanoma, which probably reflects the fact that this was the first indication for PD-1 inhibitors and more people with melanoma have been treated than those with other malignancies. With the encouraging cancer response rates for immune checkpoint inhibition, it is anticipated that many more patients with varying cancers will be treated with these therapies. Additionally, combination therapy with CTLA-4 and PD-1 inhibition is being evaluated [28,29], which may increase the frequency of Type 1 diabetes and other immune-related adverse events.

Taken together, these lines of evidence indicate clinical practice guidelines are needed to screen and monitor for this adverse event [30]. Healthcare providers managing patients being treated with these therapies need to be aware of Type 1 diabetes presenting with diabetic ketoacidosis. Patients should be educated about the signs and symptoms of hyperglycaemia and diabetic ketoacidosis, along with monitoring blood glucose. Our results indicate blood glucose levels at presentation were substantially elevated and the time to Type 1 diabetes onset did not correlate to HbA_{1c}, implying a short timeframe of significant hyperglycaemia. Routine self-monitoring of blood glucose or the use of continuous glucose monitoring may be needed to identify the initial elevations in blood glucose. Additionally, assays that evaluate specific immune cells involved in Type 1 diabetes pathogenesis are needed to understand the mechanisms of immune checkpoint inhibitor-induced Type 1 diabetes and provide a framework in which to test therapies to prevent this unwanted side effect.

In conclusion, the rapid onset of Type 1 diabetes can result when manipulating the immune system to target tumour cells with the use of immune checkpoint inhibitors. Future prospective clinical studies are warranted to screen patients receiving these therapies for risk factors associated with Type 1 diabetes onset, which will help lessen the risk of life-threatening diabetic ketoacidosis.

Competing interests

None declared.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. PubMed search strategy with text words.

Table S2. Cases of immune checkpoint inhibitor-induced Type 1 diabetes (*n*=71).

Table S3. Methodological quality assessment of reported cases.

Supplemental References.