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**Annales
d'Endocrinologie**
Annals of Endocrinology

Annales d'Endocrinologie xxx (2018) xxx–xxx

Consensus

Expert opinion on immunotherapy induced diabetes

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Abstract

Immunotherapy often incurs side-effects, mainly involving the skin, digestive tract and endocrine system. The most frequent endocrine side-effects involve the pituitary and thyroid glands. Cases of insulin-dependent diabetes, whether autoimmune or not (type 1 or 1B) have been reported with PD-1/PD-L1 inhibitors, alone or in association with anti-CTLA-4 antibodies, and were systematically associated with sudden-onset insulinopenia, frequently leading to ketoacidosis or fulminant diabetes, requiring first-line insulin therapy. This adverse effect has not so far been reported with anti-CTLA-4 monotherapy.

Recommendations

- R1. In patients receiving anti-PD-1 or anti-PD-L1 treatment, blood glucose should be assayed immediately in case of onset of polyuropolydipsic syndrome, weight loss or clinical signs of ketoacidosis, with HbA_{1c} assay in case of pathologic findings. Anti-GAD antibodies should be screened for in first line, to establish the auto-immune origin of the diabetes; if absent, anti-IA2 and anti-ZnT8 antibodies may be screened for. Blood lipase should be assayed in clinical fulminant diabetes. Pancreatic imaging is not indicated at diagnosis.
- R2. As anti-PD-1/PD-L1-induced diabetes may be fulminant, with severe insulinopenia, emergency first-line multi-injection insulin therapy should be initiated, with treatment and education in a specialized center or by a mobile diabetology team. The HbA_{1c} target is < 8.0%. There are no other treatment options for immunotherapy-induced diabetes.
- R3. Onset of diabetes under anti-PD-1 or anti-PD-L1 immunotherapy does not contraindicate continuation of treatment, although it may be interrupted for a few days in severe situations.
- R4. Systematic fasting glucose and HbA_{1c} assay is recommended ahead of any anti-PD-1 or anti-PD-L1 immunotherapy, to screen for pre-existing diabetes, defined by fasting glucose > 1.26 g/L, and/or glycemia > 2 g/L at any time of day in case of polyuria, and/or HbA_{1c} ≥ 6.5%.
- R5. Education should be ensured for patients undergoing anti-PD-1 or anti-PD-L1 immunotherapy, to recognize inaugural symptoms of diabetes (polyuropolydipsic syndrome, weight loss) or ketoacidosis (vomiting, digestive disorder).
- R6. In patients undergoing anti-PD-1 or anti-PD-L1 immunotherapy, fasting glucose should be assayed at each course of treatment during the first 3 months, then every 3 months or urgently in case of onset of clinical signs.
- R7. In case of diabetes pre-existing anti-PD-1 or anti-PD-L1 immunotherapy, glucose self-monitoring may be proposed or reinforced if already implemented.
- R8. In view of the definitive nature of the induced diabetes, treatment and monitoring should be continued after the end of immunotherapy.
- R9. Glucose monitoring is not recommended in anti-CTLA-4 therapy without associated anti-PD-1/PD-L1.

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DOIs of original articles: <https://doi.org/10.1016/j.ando.2018.07.007>, <https://doi.org/10.1016/j.ando.2018.07.002>, <https://doi.org/10.1016/j.ando.2018.07.008>, <https://doi.org/10.1016/j.ando.2018.07.001>, <https://doi.org/10.1016/j.ando.2018.07.003>, <https://doi.org/10.1016/j.ando.2018.07.004>, <https://doi.org/10.1016/j.ando.2018.07.005>

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<https://doi.org/10.1016/j.ando.2018.07.006>

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Please cite this article in press as: Smati S, et al. Expert opinion on immunotherapy induced diabetes. Ann Endocrinol (Paris) (2018), <https://doi.org/10.1016/j.ando.2018.07.006>

1. Epidemiology

Hyperglycemia is not mentioned as being a possible side-effect of anti-PD-L1 treatment in most phase II trials [1,2]. A few clinical trials reported occasional cases [3–6]. Reports are mainly of isolated cases or of small series with onset of diabetes under immunotherapy

A German retrospective study included 496 melanoma patients in 15 health-care centers in Germany and Switzerland, treated by nivolumab or pembrolizumab (a PD-1 inhibitor) [7]. Four patients (0.8%) developed diabetes: 1 male and 2 females receiving nivolumab with onset respectively 3 and 6 weeks after treatment initiation, and 1 female receiving pembrolizumab with diagnosis at 3 weeks. Onset was sudden, with inaugural symptoms of thirst, vomiting, and ketoacidosis with glucose elevation. None of the 4 showed remission of diabetes at end of immunotherapy; they were treated by basal-bolus multi-injection insulin therapy.

An Australian team reported a series of 177 patients receiving anti-PD-1 or anti-PD-L1. A single 58-year-old male, receiving ipilimumab and pembrolizumab, developed diabetic ketoacidosis 9 weeks after treatment initiation, but without anti-GAD, anti-IA-2 or anti-ICA antibodies and with fairly low HbA_{1c} at 6.8%, corresponding to the criteria for fulminant diabetes [8,9]. Incidence was thus estimated at 0.6% in this population [10]. The review by Byun et al. included several clinical trials, with overall 0.4% incidence of diabetes: i.e., 3 out of 766 patients [5]. Incidence was similar in the review by Sznol et al. [11]. Finally, a recent study reported a prevalence of 0.9% among 2,960 patients treated by immunotherapy [12].

2. Pathophysiology

Experimental data on the molecular mechanisms underlying onset of diabetes under PD-1/PD-L1 inhibitors and/or anti-CTLA-4 are sparse. PD-L1 is expressed in pancreatic islets, and PD-1/PD-L1 interaction seems to play a protective role against autoimmune diabetes, inhibiting activation of autoreactive T cells [13].

The involvement of PD-1 inhibitors in onset of autoimmune diabetes was demonstrated in NOD (non-obese diabetic) mouse models, as frequently used to study autoimmune diabetes [14]. NOD mice develop insulinitis at 4–5 weeks of age, with selective destruction of β cells and onset of diabetes as of 12 weeks. Incidence of diabetes is 60–80% in females and 20–30% in males at 40 weeks [15]. In autoimmune diabetes, PD-1 and its ligand PD-L1 play an important role in regulating T cell activation and in peripheral tolerance. Precise pathophysiology is poorly known; CTLA-4 reduces T cell activation early in the immune response [16], while PD-1 inhibits T cells at later stages in peripheral tissue [17,18]. Interestingly, anti-PD-1 or anti-PD-L1 antibody injection triggered onset of diabetes in NOD mice, at just a few days on average after injection; at 10 weeks of age, 82.4% and 76.5% of NOD females developed diabetes 6 days after injection of anti-PD-L1 and anti-PD-1 antibodies, respectively, versus 20% in control NOD mice without injection [14]. In the same study, no mice developed diabetes after anti-CTLA-4 antibody

injection. Results were similar in males, for all antibodies (PD-1, PD-L1 or CTLA-4). Histologic analysis of the pancreas found massive destructive insulinitis in NOD mice receiving anti-PD-1 or anti-PD-L1 antibodies, whereas controls of the same age showed only slight pancreatic islet inflammation. Onset of diabetes did not correlate with presence of anti-insulin auto-antibodies.

It has also been hypothesized that the intestinal microbiota may represent a risk factor for adverse autoimmune effects. Preliminary preclinical and clinical data suggest an association between certain intestinal bacterial species and immunotherapy efficacy [19,20]. Two retrospective studies suggested that *Bacteroidetes phylum* predominance reduces the risk of ipilimumab-induced colitis [21,22]. Pathophysiology is not known, and there have been no studies modulating the intestinal microbiota by diet, probiotics or antibiotics to assess impact on the efficacy and tolerance of immunotherapy. Further studies are needed to confirm the role of the microbiota in the pathophysiology of immunotherapy-induced diabetes.

3. Clinical presentation

Clinical presentation includes the classic type-1 diabetes symptoms of insulinopenia: polyuria, polydipsia and asthenia [11]. Diagnosis is confirmed biologically by clear hyperglycemia. The most severe forms, which are the majority, associate ketoacidosis. Antibodies against pancreatic β cells are not found systematically at diagnosis. Pancreatic exocrine function has not been systematically explored, but a recent report of a case of nivolumab (anti-PD1) induced diabetes showed deficits in both insulin and glucagon, with pancreatic exocrine deficiency (asymptomatic low fecal elastase level) [23].

The 33 cases reported in the literature [23–47] comprised 14 females and 19 males with autoimmune diabetes following anti-PD-1/PD-L1 antibody treatment. Twenty-one (64%) showed inaugural ketoacidosis, and 4 showed hyperglycemia associated with hyperketonemia without acidosis. Diabetes was diagnosed at a median 7 weeks after initiation of PD-1 or PD-L1 inhibitors, the latest onset being at 20 months. Antibodies were found in 18 patients (55%), in whom anti-GAD antibodies were systematic. Three of the 33 cases had history of diabetes pre-existing immunotherapy; 2 with type-2 diabetes [27,34] developed ketoacidosis associated with anti-GAD antibodies, and the third patient showed aggravated diabetes related to pancreatopathy without ketoacidosis or antibodies [46]. In the recent largest reported study (27 patients), mean age at diagnosis was 66 years; ketoacidosis was reported in 57% cases; 42% of the patients had evidence of pancreatitis in the peridiagnosis period; mean blood glucose was 6.53 g/L, mean HbA_{1c} was 7.95%, and C-peptide was very low [12].

For diagnosis, in practice we recommend assessing fasting glycemia during the first oncology follow-up consultations (first 3 months), and ketonemia or ketonuria in case of glycemia > 2.50 g/L. In case of decompensated ketosis, the patient should be admitted to screen for ketoacidosis and/or hydroelectrolytic disorder. HbA_{1c} should be assayed in case of pathologic glycemia. Anti-GAD antibodies should be screened for in first line; if absent, screening may be performed for

anti-IA2, anti-insulin and ZnT8 antibodies. Blood lipase may be assayed in case of suspected fulminant diabetes (ketoacidosis with normal or only slightly elevated HbA_{1c}). Pancreatic imaging is not indicated for diagnosis.

R1. In patients receiving anti-PD-1 or anti-PD-L1 treatment, blood glucose should be assayed immediately in case of onset of polyuropolydipsic syndrome, weight loss or clinical signs of ketoacidosis, with HbA_{1c} assay in case of pathologic findings. Anti-GAD antibodies should be screened for in first line, to establish the auto-immune origin of the diabetes; if absent, anti-IA2 and anti-ZnT8 antibodies may be screened for. Blood lipase should be assayed in clinical fulminant diabetes. Pancreatic imaging is not indicated for diagnostic purposes.

4. Treatment

All reported cases received insulin therapy by multiple injections. Treatment begins in a specialized endocrinology-diabetology department to adjust insulin dose and start therapeutic education. Regular follow-up in diabetology consultation is then recommended, with an initial target of HbA_{1c} < 8.0%. In one report, a 60-year-old male treated by pembrolizumab for melanoma with onset of ketoacidosis-type diabetes 5 weeks before treatment was managed by corticosteroids, without improvement in diabetes [39]; corticotherapy is not indicated. Immunotherapy should be continued while insulin therapy is introduced and diabetes is treated, except in severe cases in which immunotherapy may be interrupted for a few days.

R2. As anti-PD-1/PD-L1-induced diabetes may be fulminant, with severe insulinopenia, emergency first-line multi-injection insulin therapy should be initiated, with treatment and education in a specialized center or by a mobile diabetology team. The HbA_{1c} target is < 8.0%. There are no other treatment options for immunotherapy-induced diabetes.

R3. Onset of diabetes under anti-PD-1 or anti-PD-L1 immunotherapy does not contraindicate continuation of treatment, although it may be interrupted for a few days in severe situations.

5. Monitoring

5.1. Pre-treatment monitoring

Glucose and HbA_{1c} should be assayed before initiation of treatment by anti-PD-1 or anti-PD-L1 antibodies, to screen for pre-existing hyperglycemia.

R4. Systematic fasting glucose and HbA_{1c} assay is recommended ahead of any anti-PD-1 or anti-PD-L1 immunotherapy, to screen for pre-existing diabetes, defined by fasting glucose > 1.26 g/L, and/or glycemia > 2 g/L at any time of day in case of polyuria, and/or HbA_{1c} ≥ 6.5%.

Given the often fulminant-like diagnosis, patient education is important, to recognize inaugural symptoms of diabetes: polyuropolydipsic syndrome, vomiting, abdominal pain.

R5. Education should be ensured for patients undergoing anti-PD-1 or anti-PD-L1 immunotherapy, to recognize inaugural symptoms of diabetes (polyuropolydipsic syndrome, weight loss) or ketoacidosis (vomiting, digestive disorder).

5.2. During treatment

Regular monitoring of blood glucose in oncology consultation is recommended, even if this does not systematically diagnose or predict onset of diabetes in the meantime, given the sudden nature of onset. Diagnosis should also be considered in case of any clinical suspicion, with emergency glucose assay.

R6. In patients undergoing anti-PD-1 or anti-PD-L1 immunotherapy, fasting glucose should be assayed at each course of treatment during the first 3 months, then every 3 months or urgently in case of onset of clinical signs.

Data are sparse for patients with diabetes pre-existing immunotherapy. Nevertheless, capillary glycemia monitoring should be stepped up once immunotherapy begins.

R7. In case of diabetes pre-existing anti-PD-1 or anti-PD-L1 immunotherapy, glucose self-monitoring may be proposed or reinforced if already implemented.

5.3. Termination of immunotherapy

No cases of remission of diabetes at termination of immunotherapy have been reported.

R8. In view of the definitive nature of the induced diabetes, treatment and monitoring should be continued after the end of immunotherapy.

6. Predictive factors

Risk factors for onset of diabetes are unknown. A study of 453 patients treated by ipilimumab for melanoma found no associations between genotype (major histocompatibility complex HLA (human leukocyte antigen) locus) and autoimmune adverse effects [48]. Larger genome association studies are needed to determine relations between genetic factors and autoimmune adverse effects [49]. In most reported cases, patients with pre-treatment glycemia assay were euglycemic. Presence of other autoimmune diseases is non-predictive of onset of diabetes.

No cases have been reported of onset of diabetes under anti-CTLA-4 monotherapy [50].

R9. Glucose monitoring is not recommended in anti-CTLA-4 therapy without associated anti-PD1/PD-L1.

7. Impact on prognosis

No studies have specifically dealt with prognosis of cancer in case of onset of immunotherapy-induced diabetes.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgments

The text was read over and commented on by Pr. LARGER, Pr. THIVOLET and Pr. VALERO, whom the authors especially thank for their criticisms and suggestions.

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