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Abstract

Acute type 1 diabetes (AD1) is a rare but definitive immune related adverse event associated with anti-PD1. Most of reported cases are close to what has been described as “fulminant type 1 diabetes”. We **sought** to determine **wheither** anti-PD1 could impair glycoregulation and weither occurrence of AD1 could be anticipated by prior glycemic changes. Fasting glycaemia collected before, under and after treatment in melanoma patients treated with anti-PD1 over a period of 36 months were retrospectively analyzed. Glycemic trend analyses was performed using linear regression analysis. 1470 **glucose values** were monitored in 163 patients treated for a mean duration of 5.96 months. Three patients developed an AD1 (1, 84%). Two other cases were observed in the same period in a still blinded trial of anti-PD1 vs Ipilimumab. All cases of AD1 occured in patients with a normal pretreatment glycaemia and there was no detectable drift of glycaemia prior to ketoacidosis onset. In 4 of the 5 cases of AD1, HLA subgroups were DRB01* 03 or 04 known to increase type 1 diabetes risk in general population.In the 28 patients with preexisting type 2 diabetes, there was a slight trend for glycaemia increase with anti-PD1 infusions (0.05 mmol/L/infusion p=0.004). In the 132 patients with normal pretreatment glycaemia, there was a slight trend for a decrease of glycaemia with anti-PD1 infusions (-0.012/mmol/L/infusion p=0.026). **These data suggest that the monitoring of glycaemia under anti-PD1 cannot help to anticipate AD1, and there is no general tendency to glycemic disorder**. HLA-genotyping before treatment may help to focus surveillance in patients with the HLA DRB1*03/04 group.

Key words: anti-PD1, melanoma, diabetes, glycaemia, immune related adverse event, HLA

INTRODUCTION

The development of new immunotherapies with check point inhibitors including anti-CTLA4 antibodies and more recently anti-PD1 antibodies has dramatically improved the **prognosis** of metastatic melanoma [1–5]. Anti-PD1 have also demonstrated efficacy in many other malignancies like non-small cell lung cancer, renal cell carcinoma, head and neck squamous cell carcinoma and relapsing Hodgkin lymphoma.

Many immune-related adverse events (IRAE) have been reported with checkpoint-inhibitors including dermatitis, enterocolitis, hepatitis, thyroiditis, hypophysitis **as well as some less frequent but potentially life threatening rare AEs** [6,7]. In the context of an increasing number of patients exposed to these drugs, management of these IRAEs has become a priority and specific guidelines have been established [6]. While no warning signal for diabetes induced by checkpoint inhibitors has been detected during the clinical trials, several cases of acute insulin-dependent type 1 diabetes (AD1) have been recently reported under anti-PD1, and anti- PDL1 antibodies [8–10], and more recently under **the anti-CTLA4 and anti-PD1 combination** [11].

The exact mechanisms of these acute insulin-dependent diabetes under anti-PD1 therapies is currently unknown. Evidence that blockade of PD1-PDL1 checkpoint can accelerate the emergence of autoimmune diabetes in the non-obese diabetic mouse-model [12] suggests it may play a role in protecting against the development of autoimmune diabetes. **Anti-Glutamic Acid Decarboxylase (GAD) autoantibodies or Insulin auto antiboides (IAA)** have been identified in approximatively half of the anti-PD1 induced AD1 [7,8,11,17–21]. Several reported cases share close similitudes with the “fulminant type 1 diabetes” frequent in East Asia [22]: i) abrupt onset of ketoacidosis, ii) low HbA1c value despite a high plasma glucose level iii) absence of insulin secretion capacity after glucagon test. This brutal onset suggests a drastic immune reaction against β-cell.

Apart from “fulminant diabetes”, a case of diabetic ketoacidosis with insulin requirement has also been reported in a patient who had preexisting type 2 diabetes controlled with metformin [17], suggesting that some patients with preexisting type 2 diabetes might become more difficult to equilibrate under anti-PD1.

In order to determine whether anti-PD1 could impair glycoregulation in more patients than expected, especially in those with preexisting type 2 diabetes, and whether AD1 could be anticipated by prior glycaemic changes we retrospectively analyzed blood glucose samples of a series of 163 consecutive patients treated by anti-PD1 antibodies for melanoma.

PATIENTS AND METHODS

We performed a **single institution**, descriptive study of consecutive patients treated with anti-PD1 for melanoma in the department of dermato-oncology of CHU Timone in Marseille, FRANCE **since September 2013**. Each patient gave is written consent. Data were recorded for each patient between the first anti-PD1 infusion and the date of final analysis on May 2016. Available fasting blood glucose values were collected from the hospital files and retriewed from external laboratories before (in the year preceding the treatment with anti-PD1), **under** (usually 24-72h before each infusion), and within the year after anti-PD1 discontinuation for those in whom it was discontinued. The following variables were also collected: initial and per-treatment weight changes, BMI (body mass index); personal or familial history of type 1 or type 2 diabetes; personal history and history of autoimmune disease; previous treatment with Ipilimumab (yes or no), type of anti-PD1 administred (Nivolumab or Pembrolizumab), dosage, number of infusions, and cumulative dose of **exposure**; treatment efficacy (partial or complete response, stable disease or disease progression); date and cause of anti-PD1 discontinuation. The World Health Organization (WHO) definition was used for the diagnosis of diabetes i.e. fasting plasma glucose ≥ 7.0mmol/L [23].

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 20 (IBM SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as means ±SD or as median with range (min, max), and categorical variables are reported as count and percentages. When the distribution of differences between pairs was non-normally distributed, the Wilcoxn signed-rank test was used to compare pre and post **glycaemia** measurements. Glycemic trend analyses were performed using linear regression

analysis. All the tests were two-sided. The statistical significance was defined as $p<0.05$.

RESULTS

Population and treatment

The characterisics of the 163 consecutive patients treated with anti-PD1 over a period of 36 months are presented in table 1. **Twenty-eight patients (17.2%) had at least one elevated pre-treatment glycaemia. Twelve of these 28 patients had a known history of type 2 diabetes whereas 16 were not known to be diabetic**. No patient had a previous history of type 1 diabetes. Ninety-five patients (64%) were treated with Nivolumab and 68 (36%) with Pembrolizumab, 27 of which in the context of therapeutic trials. All patients, but 3 (1.8%) who were treated in the adjuvant setting, had a metastatic melanoma. Treatment was first-line in 109 (66.9%) patients. Fifty-four (32.9%) had previously been treated with ipilimumab. A total of 1920 infusions (1146 Nivolumab and 774 Pembrolizumab) were **administered** over the study period. The mean duration of the anti-PD1 treatment was 4.5 (0.5-40) months. Mean number of anti-PD1 infusions was 12.1 (1-53).

At the time of datalock, study treatment had been discontinued in 97 (59.5%) patients for disease-related death in 34 (35.1%), disease progression in 44 (45.4 %), complete response in 8 patients (8.2%), IRAEs in 7 patients (7.2%), and other adverse events non considered as IRAEs in 4 patients (4.1%) (Bilateral lower-limb ischemia in 1, dyspnea worsening in 1, intestinal ischemia in 1, and septic shock in 1 patient).

Fasting glycaemia in the whole cohort

Blood glucose samples were available in 160 of the 163 patients, and a total of 1470 **before, under and after**-treatment glycaemia were collected. There was a non-significant trend toward a decrease of glycaemia with anti-PD1 infusions (-0.012 mmol/L/infusions p=0.656). The median of the glycaemia did not change over the time of anti-PD1 exposure. The evolution of the median (min, max) glycaemia according to the number of anti-PD1 infusion is presented in figure1.

The patients weight did not significantly change under treatment (71.8 kg +/- 15.1 vs 71.6 kg +/- 15.1, p = 0.429, for mean pre-treatment and last available weight, respectively).

There was no difference in mean fasting glycaemia values according to the anti-PD1 molecule administred (Nivolumab or Pembrolizumab) nor to the fact that they had received ipilimumab before (data not shown).

Patients with normal glycaemia before-treatment

Among the 132 patients without known preexisting type 2 diabetes, and having normal glycaemia **before treatment**, 3 (2.22%) developed an AD1, all fullfilling the "fulminant diabetes" criteria. Figure 2 represents the evolution of median (min, max) glycaemia with successive anti-PD1 infusion in this population.

Apart from these 3 AD1, only one patient had one isolated increased glycaemia (8.7mmol/L) under anti-PD1 therapy, which may correspond to inadequate non-fasting sampling. In the 132 patients with normal glycaemia **before treatment**, there was a **statistically** significant negative but very low trend toward a decrease of glycaemia (-0.012/mmol/L/infusion (p=0.026)). **Five patients received systemic corticosteroids (1mg/kg), for IRAE management (colitis n=2, 1 skin rash n=1) or for symptomatic reason (2 cerebral edema).**

Patients with abnormal glycaemia before treatment

Twelve patients had a preexisting treated type 2 diabetes, and 16 others had pre-treatment fasting glycaemia compatible with type 2 diabetes definition (table 2). Out of the 16 who were previously untreated, only one patient required the introduction of repaglinide, whereas dietetic measures were sufficient to maintain glycaemia within the normal range in the 15 others. The 12 patients with a diagnosis of type 2 diabetes **before treatment** were respectively treated with insulin (n=5), oral hypoglycemic agents (n=15) (metformine (4), repaglinide (4), gliclazide (3), vidagliptine-metformine (1), sitagliptine-metformine (1), sitagliptine (1), glimepiride (1)). Among these 28 patients, 8 (28.6%) had at least one elevated glycaemia (>10mmol/L) under anti-PD1 therapy. Evolution of median glycaemia in this population is represented in figure 3.

Hemoglobin A1c (HbA1c) values were available only in 7 of these 28 patients. An HbA1c >7% was found in 2 patients during anti-PD1 treatment course, while their weight remained stable. **No type 2 patient not requiring insulin at baseline**

subsequently required insulin to manage hyperglycemia. Glycemic trend analysis by linear regression analysis suggested a slight increase of blood glucose values along with increasing number of infusions (0.05 mmol/L/infusion p=0.004). **Three patients received systemic corticosteroids for IRAE management (1 colitis) or symptomatic reason (2 cerebral edema).**

New onset AD1 under anti-PD1

Three cases (1.84%) of AD1 were diagnosed in the cohort: one after 2 **doses** of Pembrolizumab, and the two others after 4 and 11 doses of Nivolumab respectively. Two additional cases (n° 4 and 5) were diagnosed in patient receiving immunotherapy in blinded therapeutic trials (Ipilimumab versus Anti-PD1). **One of them (n°4) have since been unblinded and confirmed having reveived nivolumab**. As patient 5 is still blinded, we are not certain that he received anti-PD1. A summary of these 5 cases is provided in Table 3. **Briefly, all of them presented a cardinal syndrome with diabetic ketoacidosis, normal or subnormal HbA1C levels (range 6.4 to 7.6%), and collapsed C-peptide secretion. Two patients had slightly positive anti islet antigen-2 antibodies. Four patients carried a predisposition HLA DRB1*03 or HLA DRB1*04 haplotypes. Insulin therapy was initiated insulin therapy upon presentation for all patients, and they all remained insulin-dependent at this time**.

DISCUSSION

This is the first systematic study of glycaemia in patients treated by anti-PD1 in the real life setting. It does not support the idea that anti-PD1 could systematically induce glycemic disorders or make preexisting diabetes more difficult to manage despite a small trend for an increase of glycaemia along with anti-PD1 infusions. However, our data confirm the possibility of anti-PD1-induced AD1, and suggest that incidence of AD1 (1.8% in this series) could be underestimated. The glycaemia monitoring shows that AD1 cannot be anticipated by any preliminary drift in glucose metabolism. Our data also suggest that some HLA group (HLA DRB1*03/04) may be a risk marker for anti-PD1 induced AD1 in the Caucasian population.

More than 25 cases of type 1 acute diabetes, most of them diagnosed in patients treated for a melanoma, have been reported so far in the literature, 22 under anti-PD1, 1 under anti-CTLA4 and anti-PD1 combination and 3 under anti-PDL1 [7–9,11,17–21,24–30]. (Table 4). Among these reported cases, 3 patients had a personal history of autoimmune thyroiditis, like 2 of our patients, and 8 had previously been treated with ipilimumab [7,17,18,20,29,31].

The five cases of AD1 described herein fulfill the criteria of " fulminant diabetes"[22]: a sudden onset of hyperglycemia with ketoacidosis, normal or subnormal HbA1C levels and collapsed **C-peptide** secretion reflecting an absence of insulin-secreting capacity. In the Japanese population where fulminant diabetes was described, it was suspected to result from a rapid destruction of β-pancreatic cells secondary to a viral pancreatic infection [32,33] on a genetic predisposed background (DRB1 * 0405-DQB1 * 0401), [34,35]. In the present study, no previous change in glycaemia was predictive, making the anticipation of this complication impossible, a characteristic that justifies the term **fulminant**.

In the general population the annual incidence of AD1 is estimated 0.1 to 36/ 100.000 [36–38]. In our cohort, 2% of patients developed an AD1 under a mean period under treatment of 4 months, which suggests a huge incidence increase 100 to 1000 times higher compared to basic risk.

Our anti-PD1 AD1 cases lack the HLA haplotypes identified in the fuminant diabetes described **in the** Asian population. However, it is noteworthy that 4 of our 5 pts carried a HLA DRB1*03 or HLA DRB1*04 haplotypes known to be associated with a life-time risk of AD1 3 to 5 times higher than in the general population and even 20 to 40 times higher in patients carrying both the HLA DR3 and DR4 haplotypes [39]. As these haplotypes were mentioned in several other **Caucasian** cases of AD1 under anti-PD1, HLA DRB1*03 and 04 genotyping can be suspected to be a risk marker for AD1 in patients treated by anti-PD1. These data are compatible with the hypothesis that anti-PD1 could trigger AD1 in genetically predisposed patients, who would have been natural candidate to AD1 later on. The delay between the introduction of immunotherapy and the onset of AD1 ranged from one week to 12 months, suggesting that, when the genetic background is there, anti-PD1 can trigger the disease very fast.

It is noteworthy that developing an AD1 under anti-PD1 does not seem to be in itself a guarantee of successful treatment, although some results suggest some link between response to anti-PD1 and occurrence of IRAE [40]. Tumor response was documented in only 10 of the previous published cases. Some degree of response was observed in 8 of these 10 patients, as well as in 4 of our 5 cases.

When focusing on patients with a known preexisting diabetes, or at least pretreatment increased glycaemia compatible with a type 2 diabetes, we found a estimated pre-treatment prevalence of diabetes at 17.1% for a mean age of 65.2 years, which is quite similar to the prevalence in the French epidemiological study OBEPI [41]. Linear regression analysis in these patients suggests a slight increase (0.05mmol/L per infusion) along with increasing anti-PD1 infusions, but only one patient required the introduction of a new antidiabetic treatment. It should be noticed that the weight of patients did not either change significantly under anti-PD1 treatment. All these observations are not suggestive of a direct effect of anti-PD1 on glucose metabolism. The slight trend for an increasing glycaemia in patients with a preexisting glycemic disorder might result from a lower ability to control glycemic changes induced by many factors other than anti-PD1 treatment: impact of the tumor load on the general metabolism, indirect consequences of other immune-related complication, differences in dietary behavior, supportive treaments including steroids, etc.

In patients with normal pretreatment glycaemia, the trend is so low that it can be considered negligible.

The limit of our work is related to its retrospective character, and the fact that we did not have systematically access to HbA1c results. Nevertheless, no case of AD1 could be missed, and the study of blood glucose values does not suggest that we could find different results with a prospective study or prospective HbA1c collection. The advantage of this cohort is that it is not biased by any selection on disease severity, age and general status. **As steroids can potentially affect glycemic levels, it is important to notice that only eight patients were treated with systemic steroids to manage irAE or symptomatic cerebral oedema.**

Better determining the monitoring of asymptomatic individuals under anti-PD1 therapy has crucial cost and care implications. When investigating the relationship between asymptomatic grade 3 or higher increases in amylase and/or lipase and pancreatitis in melanoma patients who received a combination of nivolumab + Ipilimumab, Friedman and collegues [42] found only two cases of pancreatitis, representing roughly 20% of patients with grade 3 or higher amylase, or amylase lipase elevations. Our data suggest that close monitoring of glycaemia in all patients treated by anti-PD1 is useless since there was no general tendency to glycemic disorder and since AD1 cannot be anticipated from blood glucose monitoring. Furthermore, for type 2 diabetic patients, there is no reason to change the regular monitoring of their diabetes under anti-PD1 therapy. From the practical point of view, it is important to sensitize practitioners to the risk of a sudden severe ketosic decompensation in patients treated with anti-PD1, but also to inform patients on the usual symptoms, since misdiagnosis or delayed management can be fatal. HLA-genotyping before treatment may be useful to focus surveillance in patients with the HLA DRB1*03/04 group. Conversely, it would not be sensible to contraindicate anti-PD1 for these patients in the context of a deadly metastatic disease, but it may be cautious to exclude these groups from adjuvant treatment with anti-PD1.

The occurrence of IRAE under anti-PD1 being potentiated by use of immunotherapy such as anti-CTLA4 antibodies, it will therefore be necessary to be particularly vigilant and reactive in patients receiving combination or sequence of anti-PD1 and other immune-active agents.

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Figure legends

Figure 1: Whole population (n=160): Median (min, max) glycaemia with successive anti-PD1 infusions

Figure 2: Patients with normal glycaemia before treatment (n=132): evolution of median (min, max) glycaemia with successive anti-PD1 infusions.

Figure 3: Patients with abnormal glycaemia before treatment (n=28): evolution of median (min, max) glycaemia with successive anti-PD1 infusions.