Immune checkpoint therapy and type 1 diabetes

Hiroshi Ikegami¹ · Yumiko Kawabata¹ · Shinsuke Noso¹

Received: 23 June 2016 / Accepted: 26 June 2016 / Published online: 5 July 2016
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Abstract Type 1 diabetes is caused by destruction of insulin-producing beta cells of the pancreas. The etiology of type 1 diabetes is immune-mediated by either an organ-specific autoimmune mechanism in autoimmune type 1 diabetes or a still unknown but probably immune-mediated mechanism in fulminant type 1 diabetes. Immunomodulation is therefore expected to accelerate or inhibit type 1 diabetes. Recent progress in anti-cancer therapy by immune-checkpoint blockade, such as anti-PD-1 and anti-CTLA4 monoclonal antibodies, has markedly improved the prognosis of patients with advanced cancers. These drugs activate anti-tumor immunity by blocking inhibitory signals of T lymphocytes. Activation of immunological pathways, however, is expected to accelerate immune-mediated diseases. In fact, the development of autoimmune-thyroid diseases and type 1 diabetes, including fulminant type 1 diabetes, has been reported in patients treated with immune checkpoint blockers. The development of fulminant type 1 diabetes is a major concern because of its abrupt onset and very rapid progression, leading to death unless proper treatment is initiated immediately after diagnosis. In this review, the development of type 1 diabetes with immune-checkpoint therapy and its etiological background are discussed.

Keywords Type 1 diabetes · Fulminant type 1 diabetes · Autoimmune disease · Immune checkpoint · Programmed death 1 (PD-1) · Cytotoxic T-lymphocyte associated protein 4 (CTLA4)

Introduction

Type 1 diabetes is a multifactorial disease caused by a complex interaction of genetic and environmental factors [1]. The etiology of type 1 diabetes is immune-mediated, through mostly organ-specific autoimmunity against insulin-producing beta cells of the pancreas [1]. Immunomodulation is therefore expected to accelerate or inhibit type 1 diabetes. In fact, acceleration of type 1 diabetes by interferon therapy and protection against type 1 diabetes by immune suppression have been reported [2, 3]. Recent progress in anti-cancer therapy by immune-checkpoint blockade, such as anti-PD-1 and anti-CTLA4 monoclonal antibodies, has markedly improved the prognosis of patients with advanced cancers [4]. These drugs activate anti-tumor immunity by blocking inhibitory signals of T lymphocytes [5]. Activation of immunological pathways, however, is expected to accelerate immune-mediated diseases. In fact, the development of autoimmune thyroid diseases and type 1 diabetes, including fulminant type 1 diabetes, has been reported [6]. Fulminant diabetes is a subtype of type 1 diabetes, characterized by very rapid disease progression [7, 8]. The development of fulminant type 1 diabetes is a major concern, because death is likely to occur unless proper treatment is initiated immediately after diagnosis due to very rapid disease progression [8]. In this review, the development of type 1 diabetes with immune-checkpoint therapy and its etiological background is discussed.

Development of immune-mediated disease in patients treated with anti-PD-1 antibody

We have recently been consulted by dermatologists and oncologists in our hospital regarding immune-mediated endocrine diseases in patients treated with an anti-PD-1

✉ Hiroshi Ikegami
ikegami@med.kindai.ac.jp

¹ Department of Endocrinology, Metabolism and Diabetes, Kindai University Faculty of Medicine, 377-2 Ohno-higashi, Osaka-sayama, Osaka 589-8511, Japan

antibody, nivolumab. The first cases were the development of autoimmune thyroid diseases in two patients with advanced melanoma treated with nivolumab [9]. The third case was the development of type 1 diabetes in a patient treated with anti-PD-1 antibody. A male patient in his 70s had been treated with nivolumab without any adverse effect for 9 months until he developed general fatigue, thirst and polyuria 2 or 3 days before attending our hospital for treatment with nivolumab. Laboratory tests on the day of the visit showed marked hyperglycemia [plasma glucose (PG) 593 mg/dl] and ketosis [3-hydroxybutyrate 730 μ mol/l (normal range <85)]. He was admitted, and insulin treatment was started. Insulin secretory capacity assessed by glucagon stimulation test after recovery from ketosis showed that his endogenous insulin secretion was completely abolished (<0.02 ng/ml before and after glucagon stimulation). Pancreatic enzyme levels (amylase, lipase and elastase) were all increased, and islet-related autoantibodies (GAD, IA-2 and ZnT8 Abs) were all negative. From these data, other than the higher level of HbA1c (9.2 %) than the diagnostic criterion (<8.7 %), fulminant type 1 diabetes was suspected [10]. It was fortunate for him that his regular visit to the hospital for nivolumab treatment was scheduled only 2 days after he noticed the symptoms of thirst and polyuria. In view of the abrupt onset and very

rapid progression of the disease, as evidenced by the complete loss of endogenous insulin soon after its onset, if his visit had been scheduled later, he might have suffered diabetic ketoacidosis and coma, leading to a life-threatening situation.

The development of type 1 diabetes has been reported in 13 patients, including 5 suspected cases of fulminant type 1 diabetes, treated with nivolumab in Japan from 4 July 2014 to 15 May 2016 (Table 1). Although not all cases with type 1 diabetes are reported and the full details of each patient are not available, the estimated frequency of type 1 diabetes is as high as 0.20 % based on the estimated number of patients treated with nivolumab ($n = 6346$) (data from website: <https://www.opdivo.jp/>) in 22 months, corresponding to an incidence of 110/100,000 persons/year, which is much higher than reported incidences of type 1 diabetes in Japan (1.4–2.2/100,000 persons/year) [11]. Of note is the very high percentage, as high as 40 % (5/13), of fulminant type 1 diabetes in nivolumab-associated type 1 diabetes. The abrupt onset and rapid progression of fulminant type 1 diabetes in patients treated by oncologists who are not familiar with fulminant type 1 diabetes are major concerns, because a life-threatening situation due to ketoacidosis and coma may occur, leading to death in the worst cases. The Japan Diabetes Society and the Japanese

Table 1 Type 1 diabetes associated with anti-PD-1 monoclonal antibody (nivolumab) therapy (as of 31 May 2016 from website <https://www.opdivo.jp/>)

	Sex	Age ^a	Type of diabetes ^b	Onset ^c (days)	Ketosis/ ketoacidosis	PG (mg/dl)	HbA1c (%)	C-peptide (ng/ml)	GAD Ab	Corresponding case number ^d
1	F	70s	Fulminant type 1	122	DKA ^e	571	7.0	< ^g	(–)	#18 (#2)
2	F	60s	Fulminant type 1	130	DKA	450	5.8	0.7	(–)	#52 (#3)
3	F	50s	Type 1	341	ketosis	580	8.0	1.0	(–)	#111 (#1)
4	F	Unknown	Type 1	NA ^f	DKA	NA	NA	NA	NA	#119 (#4)
5	F	60s	Fulminant type 1	119	DKA	531	7.6	0.06	(–)	#128 (#5)
6	F	60s	Type 1	169	NA	539	6.6	0.25	(–)	#161 (#6)
7	F	60s	Type 1	191	DKA	NA	NA	NA	NA	#198
8	M	70s	Type 1	NA	NA	NA	NA	NA	NA	#214
9	M	70s	Type 1	NA	NA	NA	NA	NA	NA	#215
10	M	40s	Fulminant type 1	39	NA	NA	NA	NA	NA	#325
11	M	30s	Type 1	12	NA	NA	NA	NA	NA	#392
12	M	50s	Fulminant type 1	72	NA	NA	NA	NA	NA	#563
13	F	70s	Type 1	117	DKA	NA	NA	NA	NA	#605

^a Exact age is not specified

^b According to self-report by doctors

^c Days after initiation of nivolumab therapy

^d Case numbers on official website of company (<https://www.opdivo.jp/contents/pdf/open/illness.pdf>). In parentheses are case numbers on the website with details of patients with type 1 diabetes (<https://www.opdivo.jp/contents/pdf/open/guide.pdf>)

^e DKA diabetic ketoacidosis

^f Data not available

^g Below detection limit

Society of Medical Oncology, therefore, jointly announced a warning on 29 January 2016 [12] based on a request by the Ministry of Health, Welfare and Labor, Japan. In addition, the Committee on Type 1 Diabetes of the Japan Diabetes Society announced recommendations on how to diagnose and treat new-onset type 1 diabetes in patients treated with immune checkpoint inhibitors on 18 May 2016 [13].

Development of fulminant type 1 diabetes in different ethnic groups

Type 1 diabetes associated with immune-checkpoint therapy has been reported not only in Japan, but also in other countries [6, 14–17] (Table 2). In particular, fulminant type 1 diabetes has been reported in a Caucasian subject treated with an anti-PD-1 antibody, pembrolizumab [6]. Marked differences in the frequencies of fulminant type 1 diabetes are well recognized [8]. Fulminant type 1 diabetes is relatively common in Japan and East Asian countries, while it is very rare in Caucasian subjects [8]. The development of fulminant type 1 diabetes in Caucasian subjects, who are otherwise resistant to fulminant type 1 diabetes, treated

with anti-PD-1 antibody suggests the importance of the PD-1 pathway in the etiology of fulminant type 1 diabetes.

PD-1 (programmed cell death 1): a negative regulator of the immune reaction

Fine tuning of the immune reaction is essential for protection of the body from infection, malignant tumors and immune-mediated diseases. Immune reaction to foreign antigens such as viruses as well as altered self-antigens such as tumors is both positively and negatively regulated. The main pathway is the presentation of antigen peptide in the context of class II molecules of the major histocompatibility complex (MHC) by antigen-presenting cells (APC), such as dendritic cells, and recognition of these antigen-MHC complexes by the T cell antigen receptor (TCR) on the surface of T lymphocytes (signal 1) (Fig. 1). In addition to signal 1, recognition of ligands, termed B7, on APC by a receptor, termed CD28, on T cells is necessary to initiate the immune reaction (signal 2) (Fig. 1). These positive signals are negatively regulated by several molecules, so as to limit too much activation, prevent damage of normal tissues and eventually stop the immune

Table 2 Type 1 diabetes associated with anti-PD-1 monoclonal antibody therapy (cases from published literature)

	Sex	Age	Type of diabetes	Anti-PD-1 Ab	Onset ^a	Ketosis/ ketoacidosis	PG (mg/dl)	HbA1c (%)	C-peptide (ng/ml)	GAD/titer	References
1	F	55	Type 1 (fulminant?) ^b	Nivolumab ^g	5 months	DKA ^c	532	6.9	<0.1	(–)	[14]
2	F	83	Type 1 (fulminant?) ^b	Nivolumab	<1 month	DKA	350	7.7	<0.1	(+)/1.1	[14]
3	M	63	Type 1	Nivolumab	4 months	NA ^d	247, 340	8.2	1.3	(+)/1.2	[14]
4	M	58	^e Type 1	Nivolumab	1 week	DKA	749	9.7 ^e	<0.1, 0.6	(+)/13819	[14]
5	F	64	Type 1	Pembrolizumab	<1 month	Ketosis	703	7.4	0.5	(–)	[14]
6	F	66	Type 1	PD-1 antibody ^f	7 weeks	DKA	752	9.4	<0.1	(+)	[15]
7	F	44	Fulminant type 1	Pembrolizumab ^g	2 weeks after 2nd ^h	DKA	908	6.85	< ⁱ	(–)	[6]
8	F	54	Type 1	Pembrolizumab ^g	9 weeks	DKA	NA	NA	NA	(+)/70.1	[16]
9	F	55	Fulminant type 1	Nivolumab	12 months	DKA	580	7.0	1.0	(–)	[17]

Case #7 is a Caucasian subject; #9 is a Japanese subject; ethnicity of other subjects is unknown

^a After initiation of therapy with anti-PD-1 antibodies

^b Could be fulminant type 1 according to diagnostic criteria (Ref. [10])

^c DKA diabetic ketoacidosis

^d Data not available in the literature

^e Treated for type 2 diabetes before initiation of anti-PD-1 therapy

^f Not specified

^g Concomitantly or soon after use of anti-CTLA4 antibody, ipilimumab

^h 2 weeks after second injection of pembrolizumab

ⁱ Below detection limit

reaction. One of these is CTLA4, a receptor expressed on T cells, which recognizes the same B7 molecules as ligands, as in the case of CD28. Thus, the same B7 molecules transmit a positive signal when recognized by a CD28 receptor, while a negative signal is transmitted when

Fig. 1 Axels and brakes in the immune reaction. Immune reaction against a certain antigen is regulated both positively (axels) and negatively (brakes). **a** Axels (positive regulation). A main pathway is the stimulation of T cells by antigen presented in the context of major histocompatibility complex (MHC) class II molecules by antigen-presenting cells (APC) and recognition of antigen-MHC class II complexes by the T cell antigen receptor (TCR) on T cells (signal 1). In addition to signal 1, a costimulatory signal induced by the interaction of the CD28 receptor on T cells with its ligands, B7 [B7.1 (CD80) and B7.2 (CD86)] (signal 2), is necessary to start the immune reaction against antigen. **b** Brakes (negative regulation). CTLA4, a receptor expressed on T cells, recognizes as ligands the same B7 molecules as those recognized by CD28 and inhibits the immune reaction at both the level of ligand recognition by competing with the same ligands as those of CD28 and the level of signal transduction in the CD28-mediated costimulatory pathway. PD-1 is another receptor expressed on T cells acting as a negative regulator of the immune reaction. Upon recognition of its ligands, PDL1 (also known as B7-H1 or CD274) and PDL2 (B7-DC or CD273), PD-1 negatively regulates the immune reaction by inhibiting the TCR signaling pathway (signal 1) through inactivation of ZAP70, a major integrator of TCR-mediated signaling. PD-1 also inhibits the CD28-mediated costimulatory pathway (signal 2) by inhibiting PI3 kinase (PI3 K). **c** Axels without brakes. Inhibition of PD-1 and CTLA4 by anti-PD-1 and anti-CTLA4 antibodies strongly activates the immune reaction, leading to a beneficial effect on cancers and malignant tumors, but a harmful effect on autoimmunity and immune-related diseases, including type 1 diabetes

recognized by a CTLA4 receptor, providing fine tuning of the immune reaction, as with the axels and brakes of a car.

Another negative regulator is programmed cell death 1 (PD-1), which is a receptor expressed on antigen-stimulated T cells and other immune cells [5]. PD-1 has two ligands, PD-L1 and PD-L2. Upon binding with these ligands, PD-1 negatively regulates the immune reaction by inhibiting the TCR signaling pathway (signal 1), which inactivates ZAP70, a major integrator of TCR-mediated signaling [5] (Fig. 1). These inhibitory pathways function as immune system checkpoints, negatively regulating T cell activation and thereby limiting and stopping excessive immune reactions.

Inhibition of PD-1 pathway for treatment of cancer and malignant tumors

Since inhibition of negative regulators is expected to increase the immune reaction to pathogen and tumor antigens, antibodies directed against PD-1 and CTLA-4 have been developed for the treatment of cancer and malignant tumors [4]. Another reason for the development of anti-PD-1 antibodies for anti-tumor therapy is that one of the ligands of PD-1, PD-L1, is expressed not only on immune cells, but also on many cell types, including tumor cells, and tumor cells appear to escape immune attack through their expression of PD-L1. Among these anti-PD-1

antibodies are nivolumab and pembrolizumab, fully human and humanized anti-PD-1 monoclonal antibodies, respectively. Marked improvement of advanced tumors resistant to ordinary chemotherapy, such as malignant melanoma and non-small cell lung cancer, has been achieved with anti-PD-1 antibody [18–21], and it has been approved for clinical use in Japan. In addition to currently approved diseases, application of this class of drugs to malignant tumors of other organs is under clinical trials, which is anticipated to lead to the expansion of such treatment to a wide variety of tumors [4]. Furthermore, the anti-CTLA4 monoclonal antibody ipilimumab is also in clinical use, and combination therapy of an anti-PD-1 antibody (nivolumab) with an anti-CTLA4 antibody (ipilimumab) is also approved for clinical use in the USA [22] and EU [23] and is under clinical trial in Japan (<http://www.opdivo.bmscutomerconnect.com/gateway>). Other antibodies for immune checkpoint inhibition are also in development [4].

PD-1 pathway and type 1 diabetes

Since PD-1 is a negative regulator of the immune reaction, abnormality in the PD-1 pathway was expected to cause hyperactivity of immune function, leading to the development of autoimmune diseases, such as type 1 diabetes. In fact, inhibition of the PD-1 pathway in the NOD mouse, an animal model of type 1 diabetes, was reported to accelerate type 1 diabetes [24]. Mice deficient in PD-1 were reported to develop autoimmunity against diverse target organs depending on their genetic background [25–28]. The development of type 1 diabetes was observed only when the mouse genetic background was NOD [29], suggesting that genetic susceptibility to type 1 diabetes is necessary for the development of type 1 diabetes in PD-1 deficiency. Since PD-1 negatively regulates the immune reaction at the level of signal 1, which is generated when T cells recognize the antigen-MHC complex through TCR (Fig. 1), the effect of PD-1 is expected to be antigen-specific. This is probably the reason why only a limited target organ is affected by autoimmune attack in PD-1 deficiency.

In humans, we previously reported the genetic association of *PDCDI*, the gene encoding PD-1, with type 1 diabetes [30]. More recently, low expression of PD-1 in T cells was reported in autoimmune type 1 diabetes, and the expression level was associated with *PDCDI* polymorphism [31]. Thus, inhibition of the PD-1 pathway by anti-PD-1 antibodies, as in the case of immune checkpoint therapy for cancer, is expected to induce type 1 diabetes. In fact, the development of type 1 diabetes has been reported as mentioned above [6, 14–17], and other autoimmune diseases, such as autoimmune thyroid diseases, myasthenia gravis and interstitial pneumonia, have also been reported

in patients treated with anti-PD-1 monoclonal antibodies [9, 32, 33].

Thus, in both animal models and humans, inhibition of the PD-1 pathway induces autoimmune diseases including type 1 diabetes, indicating the contribution of the PD-1 pathway to the development of type 1 diabetes and other autoimmune diseases. The development of fulminant type 1 diabetes surprised us, because fulminant type 1 diabetes is classified as idiopathic type 1 diabetes because of the lack of islet-related autoantibodies in most cases [7, 8] and absence of insulitis in biopsy specimens of patients [7]. Although it is still under extensive discussion whether or not fulminant type 1 diabetes is of autoimmune etiology, the consensus is that immune-mediated mechanisms are involved [8, 34, 35]. The development of both autoimmune type 1 diabetes and fulminant type 1 diabetes in patients treated with anti-PD-1 antibodies suggests the contribution of the PD-1 pathway in autoimmune as well as fulminant type 1 diabetes and that fulminant type 1 diabetes shares, at least in part, molecular mechanisms with autoimmune type 1 diabetes.

PD-1 and CTLA4 in type 1 diabetes and other autoimmune diseases

In contrast to the development of type 1 diabetes in a substantial number of patients treated with anti-PD-1 antibodies, type 1 diabetes has not been reported in patients treated with anti-CTLA4 antibodies alone, in either Japan or the USA (<http://www.yervoy.com/>). In contrast, autoimmune thyroid diseases have been reported with both anti-PD-1 and anti-CTLA4 antibody treatment. One possible explanation is the smaller number of patients treated with the anti-CTLA4 antibody ipilimumab in Japan ($n = 245$ in 6 months, data from website: https://file.bmshealthcare.jp/yervoy/pdf/side_effect0229_2.pdf) than those treated with the anti-PD-1 antibody nivolumab ($n = 6346$ in 22 months); therefore, a lower frequency of side effects, as in the case of type 1 diabetes, has not been observed. Another possibility, however, is the difference in the contribution of the PD-1 and CTLA4 pathways to the etiology of type 1 diabetes. *CTLA4* is a well-known susceptibility gene for autoimmune thyroid diseases [36]. The association of *CTLA4* with type 1 diabetes was also reported [37], but subsequent studies revealed that this association was mainly due to autoimmune thyroid diseases concomitant with type 1 diabetes [38, 39], and when type 1 diabetes was stratified by the presence or absence of autoimmune thyroid diseases, an association with *CTLA4* was observed in type 1 diabetes concomitant with AITD, but not in type 1 diabetes without AITD [38]. These data, together with the development of AITD but not type 1

diabetes with anti-CTLA4 antibody therapy, suggest that CTLA4 may not be a primary factor in the development of type 1 diabetes. Further studies with a larger number of subjects treated with anti-CTLA4 antibodies are necessary to verify this hypothesis.

Even if CTLA4 is not a primary factor in the development of type 1 diabetes, inhibition of CTLA4 accelerates the immune reaction in general; therefore, ongoing immune reaction against beta cells is expected to be accelerated. Combination therapy of anti-CTLA4 with anti-PD-1 antibodies may therefore further increase the risk of type 1 diabetes as compared with anti-PD-1 antibodies alone by accelerating the immune reaction that has already been initiated and targeted to beta cells of the pancreas. Careful observation and appropriate management are needed in patients treated with combination therapy with anti-CTLA4 and anti-PD-1 antibodies.

Future directions

Since the original diseases in which immune checkpoint inhibitors are used, advanced cancer and malignant tumors, are life-threatening conditions, these drugs are indispensable for treatment of these patients. Although type 1 diabetes, including fulminant type 1 diabetes, is also a life-threatening condition, insulin treatment can save patients and normal daily life can be continued with insulin treatment if there is early diagnosis and optimal treatment from the onset. It is therefore important for all doctors and medical staff using this class of drugs to be aware of the possibility of the development of type 1 diabetes in general, and fulminant type 1 diabetes in particular, in patients treated with immune checkpoint inhibitors. As mentioned in the warning and recommendations from the Committee on Type 1 Diabetes of the Japan Diabetes Society, symptoms and laboratory parameters should be monitored in all patients treated with immune checkpoint inhibitors, and as soon as type 1 diabetes is suspected, consultation with a diabetologist is recommended for the diagnosis and treatment of type 1 diabetes. The number of patients treated with anti-PD-1 antibodies is markedly increasing because of their efficacy and expanding application to a wide variety of malignant tumors, including treatment with combination therapy of anti-PD-1 antibodies and anti-CTLA4 antibodies. Careful monitoring and appropriate management of immune-mediated side effects, including type 1 diabetes, are therefore strongly recommended.

In addition to saving patients from life-threatening conditions due to type 1 diabetes, extensive study on the clinical and genetic background of the patients who develop type 1 diabetes with immune checkpoint inhibitors

will clarify the genetic basis and molecular pathogenesis of the disease. In particular, studies on fulminant type 1 diabetes induced by immune checkpoint inhibitors are expected to clarify the molecular mechanisms of fulminant type 1 diabetes, whose etiology is still largely unknown, leading to the development of effective methods for prevention, intervention and cure of the disease. A multicenter study on fulminant type 1 diabetes induced by immune-checkpoint inhibitors by the Committee on Type 1 Diabetes of the Japan Diabetes Society is now in progress.

Acknowledgments This study was supported by grants-in-aid for scientific research from Japan Society for the Promotion of Science (15K09404 to HI, 26461348 to YK, 26461349 to SN), a grant from the Ministry of Health, Labor and Welfare (H28-Jyunkanto-ippan-006 to HI) and a grant from Japan Agency for Medical Research and Development (16768653 to HI).

Compliance with ethical standards

Conflict of interest Authors have nothing to declare related to this review.

Ethical standards This article does not contain any studies with human or animal subjects performed by any of the authors.

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