Endocrine side effects of cancer immunotherapy

Priscilla Cukier¹, Fernando C Santini², Mariana Scaranti² and Ana O Hoff¹

¹Department of Endocrinology, Instituto do Cancer do Estado de São Paulo, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

²Department of Oncology, Instituto do Cancer do Estado de São Paulo, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

Correspondence
should be addressed
to A O Hoff
Email
ana.hoff@hc.fm.usp.br

Abstract

Immune checkpoint inhibitors have recently become a cornerstone for the treatment of different advanced cancers. These drugs, represented mainly by monoclonal antibodies anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4), anti-programmed cell death protein-1 (PD-1) and anti-PD-1 ligand molecules (PD-L1 and L2), have the ability to reactivate the immune system against tumor cells, but can also trigger a myriad of autoimmune side effects, termed immune-related adverse events (irAEs). In particular, there are a number of endocrine-related irAEs. Current data from clinical trials show increased incidence of hypophysitis with CTLA4 inhibition and thyroid dysfunction with PD-(L)1 blockade. In addition, a few cases of type 1 diabetes mellitus and primary adrenal insufficiency have been reported. We discuss the incidence, clinical manifestations, diagnosis and management of immune-related endocrinopathies in this highly complex context of oncological patients in need of immunotherapies.

Key Words

- ▶ thyroid
- ▶ endocrine side effects
- ▶ cancer immunotherapy
- ▶ hypophysitis
- ▶ immune checkpoint inhibitors

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Introduction

In the past few decades, cancer therapy has advanced, with immuno-oncology emerging as an effective strategy for a variety of advanced-stage cancers (Horvat *et al.* 2015). There are a number of modalities of immunotherapy, including monoclonal antibodies (mAbs), adoptive cell therapy, immunomodulatory small molecules, oncolytic viruses, vaccines and tumor-targeting mAbs. As a whole, immunotherapy has the potential to generate or augment an immune response against cancers, offering a robust and durable response.

Most incipient tumors are eliminated by a process called immune surveillance. Cancer cells, however, can evade this immune attack through the upregulation of immune-inhibitory pathways. Immunotherapy works to suppress these immune checkpoints resulting in immune-mediated antitumor activity.

Clinical development and approval of immune checkpoint inhibitors have transformed the natural history of certain tumors. Several immune checkpoint inhibitors are already approved for treatment of different cancers by the United States Food and Drug Administration (FDA) including melanoma, non-small cell lung cancer (NSCLC), head and neck cancer, renal cell carcinoma, urothelial cancer, Merkel cell carcinoma, Hodgkin's lymphoma and mismatch-repair deficient cancers (Table 1). Of note, combination of anti-CTLA4 and anti-PD-1 is approved for cutaneous melanoma, and promising results from early phase trials have been published for other malignancies (Antonia *et al.* 2016, Hellmann *et al.* 2017).

Given that immune-inhibitory pathways have an important role in the maintenance of self-tolerance, therapeutic targeting of these pathways can lead to

Table 1 Immunotherapy monoclonal antibodies and their main indications.

	Anti-PD-1		Anti-PD-L1			Anti-CTLA4
	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab	Avelumab	Ipilimumab
Melanoma			X	X	X	
NSCLC				X	X	X
HNSCC			X	X	X	X
RCC		X	X	X	X	X
Urothelial						X
cHL	X		X	X	X	X
MSI-H	X		X	X	X	X
Merkel cell carcinoma	X	X	X	X		X

cHL, classical Hodgkin's lymphoma; HNSCC, head and neck squamous cell carcinoma; MSI-H, high microsatellite instability tumors; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma.

imbalances in immunologic tolerance, which manifest as immune-related adverse events (irAEs). A broad range of autoimmune toxicities have been reported, and nearly all organs can be affected, including skin, gastrointestinal tract, lung, kidney and heart, among others (Michot *et al.* 2016). Even immune-privileged organs such as the eye and the brain can be affected (Crews *et al.* 2015, Henderson *et al.* 2015, Yeh *et al.* 2015, Bossart *et al.* 2017). The incidence of any grade irAEs is reported to range from 15 to 90% in single agent trials (Hodi *et al.* 2010, Eggermont *et al.* 2016, Ferris *et al.* 2016, Kumar *et al.* 2017). The spectrum of autoimmune adverse events is different in the anti-CTLA4- and anti-PD-L1-treated patients. For example, thyroid diseases are more frequent with PD-1 blockade, whereas colitis and hypophysitis are more frequent with CTLA-4 blockade.

Ipilimumab, the main representative of CTLA-4 inhibitors, has been extensively studied. The incidence of irAEs is dose related, the most common ones are pruritus, diarrhea, rash, and fatigue. Grade 3–4 (severe to life-threatening) (<http://evs.nci.nih.gov/ftp1/CTCAE>) irAEs were reported in less than 5% of patients, except for diarrhea (Weber 2009, Hodi *et al.* 2010, Boutros *et al.* 2016).

Nivolumab and pembrolizumab, the best studied anti-PD-1 drugs so far, have very similar safety profiles and induce fewer adverse events than ipilimumab. The most common adverse events of any grade following treatment with anti-PD-1 therapy included fatigue, rash, pruritus and diarrhea. Potential irAEs of any grade affected primarily the skin, gastrointestinal, endocrine and pulmonary systems and were generally of a low grade. Grade 3–4 irAEs occurred in 2–3% of patients and were generally managed with withholding the drug, corticosteroids use or permanent discontinuation of the agent. In general, grade 1–2 (asymptomatic to moderate) (<http://evs.nci.nih.gov/ftp1/CTCAE>) adverse events are

managed symptomatically and usually do not require dose omission and discontinuation (Friedman *et al.* 2016).

In contrast to inhibiting PD-1, targeting PD-L1 leaves PD-L2 uninhibited, which may preserve a component of peripheral immune homeostasis. For organs like the lung, this was hypothesized to reduce the likelihood of developing severe inflammatory toxicity (Rozali *et al.* 2012). However, a recent study by Pillai and coworkers investigating 4869 patients with NSCLC treated with either PD-1 or PD-L1 inhibitors showed no significant difference in toxicity profile between them (Pillai *et al.* 2016).

Recent clinical trials investigating combination therapy with CTLA-4 and PD-(L)1 blockade has shown promising results; however, it has been associated with a higher prevalence of irAEs than monotherapy. Grade 3 or 4 adverse events were reported in up to 55% of the patients, in particular diarrhea, colitis and elevated aminotransferase levels (Hodi *et al.* 2015, Larkin *et al.* 2015).

Approximately one-quarter to one-third of the patients treated with checkpoint blockade will receive immunosuppressive therapy for the management of irAE. Data published with melanoma patients also report that overall survival and time to treatment failure were not affected by the occurrence of irAEs or the need for systemic corticosteroids (Horvat *et al.* 2015). Most irAEs occur within 3–6 months of initiation of immunotherapy, although a delayed effect of immune checkpoint antibodies cannot be ruled out, sometimes up to few years after the start of treatment (Michot *et al.* 2016).

Whether irAEs are associated with improved response of tumors to immune checkpoint blockade is still not understood, due to conflicting data. A large meta-analysis of multiple melanoma immunotherapy modalities found that development of vitiligo is associated with better progression-free survival and overall survival,

Figure 1

Suggested recommendation for biochemical evaluation and monitoring of pituitary dysfunction in patients treated with immunotherapy. [§]When using anti-CTLA4, anti-PD-(L)1 baseline and if symptoms persist on *2 years of follow-up, **high-dose steroids in patients with critical illness, in patients with severe hyponatremia, severe headache, visual abnormalities from pituitary enlargement and low-dose steroids (e.g. hydrocortisone 20–30 mg/day) with mild symptoms such as fatigue, mild headache. [§]Should be considered to selected premenopausal women. ACTH, adrenocorticotrophic hormone; FSH, follicle-stimulating hormone; fT₄, free thyroxine; LH, luteinizing hormone; mo, months; T₃, triiodothyronine; TSH, thyroid-stimulating hormone; WNL, within normal range.

with a twofold to fourfold reduction in risk of disease progression and death in patients who develop vitiligo. This trend might be due to the monitoring of patients for a longer period of time and bias resulting from extended duration of symptomatic observation (Lo *et al.* 2015, Teulings *et al.* 2015).

The aim of this review is to describe the endocrine-related adverse events associated with immunotherapies, focused on anti-CTLA-4, anti-PD-1 and anti-PD-L1, as well as to discuss their management and suggested evaluation for early diagnosis (Fig. 1). As symptoms of endocrinopathies could be nonspecific, a high degree of suspicion should be in place so that diagnosis could be confirmed and treatment could be rapidly instituted.

Brief review of the immunobiology of cancer

There are three necessary steps to mount an effective antitumor immune response: dendritic cells antigen presentation, production of protective T cell response

in the central lymphatic system and overcoming immunosuppression in the tumor microenvironment.

The initial activation of naïve T lymphocytes occurs mainly in secondary lymphoid organs, where they may encounter antigens presented by mature dendritic cells. The specific recognition of antigenic peptides, presented by the MHC, triggers TCR signaling. The co-stimulatory and co-inhibitory receptors on T cells direct T cell function and determine T cell fate. The best characterized central co-stimulatory pathway in T cell activation is represented by the engagement of CD28 with B7-1 (CD80) and B7-2 (CD86), expressed on activated antigen-presenting cells (APCs). In resting T cells, CTLA-4 binds with high affinity to B7 and can compete with CD28 to further inhibit T cell activity. This process stops the T cell from maintaining an immune response. Monoclonal antibodies (mAb) that target CTLA-4 reinvigorate proliferation of T cells, which become constitutively active.

Activated T cells will exit the lymph node and enter the tumor bed where a myriad of immunosuppressive

mechanisms coexist, represented mainly by upregulation of PD-L1 and PD-L2 on cancer cell surface. PD-1 is expressed on the surface of activated T and B lymphocytes and monocytes. Binding of PD-1 to its ligands, PD-L1 and PD-L2, inhibits the immune response. A mAb against PD-1 or PD-L1 can block this pathway and result in the upregulation of immune response and inhibition of tumor growth. Furthermore, anti-CTLA-4 mAbs might exert some of its antitumor effect in the tumor microenvironment with depletion of the T_{REG} cell population (Latchman et al. 2001, Chen et al. 2012, Boussiotis 2016).

As CTLA-4 and PD-1 regulate the immune response at different levels, one might expect that the incidence and type of the irAEs are different between anti-CTLA-4 and anti-PD-L1. Likewise, autoimmune manifestations of animals with PD-1 or CTLA-4 deficiencies are distinct (Francisco et al. 2010, Klocke et al. 2016). CTLA-4 regulates T cell activation centrally and potentially in all lymph nodes. This broad activation explains the higher frequency of irAEs after CTLA-4 blockade when compared to other checkpoint inhibitors. Of note, polymorphisms of *PD-1* and *CTLA-4* are associated with various autoimmune

conditions such as rheumatoid arthritis, Addison disease, celiac disease, Crohn's disease, thyroid disorders and type 1 diabetes (Ueda et al. 2003).

Immunotherapy-induced endocrine toxicities

Fatigue is the most frequent adverse event with immune check point blockade. Its intensity, however, is usually mild and the presence of severe fatigue should trigger an assessment for underlying disorders, such as endocrinopathies.

The spectrum of endocrine irAEs includes hypopituitarism caused by hypophysitis, primary or secondary thyroid disease, primary or secondary adrenal insufficiency, hyperglycemia due to type 1 diabetes and, more rarely, hypoparathyroidism (Table 2). The precise frequency and severity of endocrine dysfunction is not well defined, due to variations in data collection. Initially, clinical trial reports of adverse events were based on symptoms, which could be nonspecific, rather than a biochemically defined diagnosis. More recent trials, however, have increasingly introduced hormonal

Table 2 Reported frequencies of endocrine immune-related adverse events observed with immunotherapies.

Monoclonal antibodies	Endocrinopathies				
	Hypophysitis (%)	Hypothyroidism (%)	Hyperthyroidism (%)	Primary adrenal insufficiency (%)	Type 1 DM (%)
Anti-CTLA-4					
Ipilimumab ^a	1.5–17	1.5–6.8	4	0.8–1.6	NR
Tremelimumab ^b	0.4–2	2.3	0–3	1	NR
Anti-PD-1					
Nivolumab ^c	0.6–1.5	9–10.8	2.7	1	0.9
Pembrolizumab ^d	0.6–1	7–9.1	3.4–7.8	NR	0.2
Anti-PD-L1					
Avelumab ^e	NR	5	0.4	0.5	0.1
Atezolizumab ^f	0.2	2.5–4.2	0.6–1.1	0.4	0.2–0.3
Durvalumab ^g	<0.1	5.5–9.6	4.9–5.7	0.5–0.9	0.1
Combined therapy					
Nivolumab + ipilimumab ^h	4–12.8	4–27	4.3–14	4–8*	NR
Pembrolizumab + ipilimumab ⁱ	9.1	6–13.6	4.5–6	6*	NR
Durvalumab + tremelimumab ^j	NR	5.9	NR	NR	NR

*Comprises primary and secondary adrenal insufficiency.

CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed cell death protein-1; PD-L1, PD-1 ligand molecule; NR, not reported.

^aPhan et al. 2003, Attia et al. 2005, Maker et al. 2006, Downey et al. 2007, Yang et al. 2007, Weber et al. 2008, 2009, 2017, Ansell et al. 2009, Hodi et al. 2010, Ku et al. 2010, O'Day et al. 2010, Royal et al. 2010, Wolchok et al. 2010, Di Giacomo et al. 2011, Hersh et al. 2011, Sarnaik et al. 2011, Margolin et al. 2012, Altomonte et al. 2013, Slovin et al. 2013, Chiarion-Sileni et al. 2014, Kwon et al. 2014, Ryder et al. 2014, Larkin et al. 2015, Postow et al. 2015, Eggermont et al. 2016; ^bRibas et al. 2005, Camacho et al. 2009, Chung et al. 2010, Kirkwood et al. 2010, Ralph et al. 2010, Ribas et al. 2012, 2013, Sangro et al. 2013, Aglietta et al. 2014, Calabrò et al. 2015; ^cBrahmer et al. 2010, Topalian et al. 2012, Weber et al. 2013, 2015a,b, 2017, Topalian et al. 2014, Ansell et al. 2015, Bauer et al. 2015, Brahmer et al. 2015, El-Khoueiry et al. 2015, Gettinger et al. 2015, Hamanishi et al. 2015, Motzer et al. 2015, Nishio et al. 2015, Paz-Ares et al. 2015, Rizvi et al. 2015b, Robert et al. 2015a; ^dHamid et al. 2013, Robert et al. 2014, Doi et al. 2015, Garon et al. 2015, Le et al. 2015, Ott et al. 2015, Ribas et al. 2015, Robert et al. 2015b, Varga et al. 2015, Reck et al. 2016, Seiwert et al. 2016; ^eDisis et al. 2015, Gulley et al. 2015, Kelly et al. 2015, Shitara et al. 2015, Yamada et al. 2015; ^fCho et al. 2013, Hamid et al. 2013, Herbst et al. 2013, Spigel et al. 2013, Powles et al. 2014, Petrylak et al. 2015, Spira et al. 2015; ^gLutzky et al. 2014, Segal et al. 2014, 2016, Iguchi et al. 2015, Rizvi et al. 2015a; ^hWolchok et al. 2013, Antonia et al. 2015a,b, Hammers et al. 2015, Hodi et al. 2015, Larkin et al. 2015, Postow et al. 2015; ⁱAtkins et al. 2015, Patnaik et al. 2015; ^jAntonia et al. 2015a,b.

screening, resulting in earlier and more accurate diagnoses (Corsello et al. 2013).

Hypophysitis and hypothyroidism are the most common endocrinopathies, seen in up to 10% of patients treated with anti-CTLA-4 and anti-PD-1/PD-L1 antibodies (Corsello et al. 2013, Topalian et al. 2014, O'Donnell et al. 2015, Eggermont et al. 2016, González-Rodríguez et al. 2016, Byun et al. 2017). The growing recognition that immunotherapy is potentially associated with endocrine-related adverse events has resulted in higher reported rates of hypophysitis, as clinical suspicion and routine laboratory testing have become a more routine practice (Albare et al. 2015, Min et al. 2015, Faje 2016). Clinical suspicion and routine hormone testing are key to the diagnosis of immune-related endocrinopathies.

Pituitary dysfunction

Anti-CTLA-4 mAbs

Pituitary dysfunction is among the most commonly reported endocrinopathies and is much more common after anti-CTLA-4 therapy than other immunotherapies (Table 2). The average incidence of ipilimumab-induced hypophysitis is 13%, ranging from 1.5 to 17% (Tables 2 and 3) (Faje et al. 2014, Faje 2016). In contrast to lymphocytic autoimmune hypophysitis, ipilimumab-induced hypophysitis occurs more frequently in men (Corsello et al. 2013, Min et al. 2015, Faje et al. 2016) and in those of an older age (Faje et al. 2014, Faje 2016), even after adjustment of melanoma incidence in male and the elderly. Other associated agents and radiotherapy can alter the risk of hypophysitis induced by ipilimumab, but data are limited (Postow et al. 2012, Stamell et al. 2013, Shahabi et al. 2015).

The time to occurrence of these endocrine abnormalities has not been routinely reported in these trials. Notwithstanding, the average time to diagnosis of hypophysitis is 9 weeks of initiation of ipilimumab. A homogeneous or heterogeneous enlargement of the pituitary with thickening of the stalk, seen at pituitary magnetic resonance imaging (MRI), is a sensitive and specific indicator of hypophysitis. These radiographic changes may be the first sign of hypophysitis, preceding hormonal disturbances and symptoms (van der Hiel et al. 2013, Faje et al. 2014). Pituitary enlargement can be mild and only apparent if compared with previous imaging study and reduces rapidly after glucocorticoid initiation in virtually all patients (Table 3).

Table 3 Ipilimumab-induced pituitary dysfunction – clinical and laboratory characteristics from three longitudinal cohorts (Faje et al. 2014, Albarel et al. 2015, Min et al. 2015).

	No. (%)
Patients	428 (100)
Hypophysitis	57 (13.3)
Male	44 (77)
Median time to diagnose after Ipilimumab initiation (weeks)	9
Pituitary enlargement	44 (78)
Visual disturbances	0 (0)
Symptoms	
Headache	27 (84)
Fatigue	21 (65)
Laboratory abnormalities at diagnosis	
Hyponatremia	22 (56)
Thyroid	52 (92)
Adrenal	40 (74)
Gonadal	42 (85)
Growth hormone (IGF-1)	6 (28)
Prolactin	
High	2 (6)
Low	29 (94)
Diabetes insipidus	0 (0)
Resolution of pituitary enlargement	40 (100)
Resolution of secondary hormonal abnormalities	
Thyroid	34 (59)
Adrenal	8 (14)
Gonadal	35 (59)
Growth hormone (IGF-1)	10 (90)
Prolactin	10 (90)

The most frequent symptoms of ipilimumab-induced hypophysitis are headache and fatigue. In contrast to lymphocytic hypophysitis, visual disturbances are rare. Despite the fact that most patients will present multiple hormone deficiencies, central hypothyroidism and secondary adrenal insufficiency remain most common, while both growth hormone and prolactin axis are generally spared. Secondary hyponatremia due to adrenal insufficiency and central hypothyroidism is frequently observed, but diabetes insipidus is rarely present. Reduction of TSH levels, indicating incipient central hypothyroidism, often occurs prior to the diagnosis of hypophysitis (Faje et al. 2014). Secondary adrenal insufficiency associated with anti-CTLA-4-related hypophysitis is usually permanent and requires lifelong steroid replacement (Albare et al. 2015) (Table 3). Some studies suggest that the development of hypophysitis may predict a better antitumor response of ipilimumab (Faje et al. 2014).

Iwama and coworkers established a murine model of secondary hypophysitis based on injections of a CTLA-4-blocking antibody (Iwama et al. 2014). CTLA-4 is expressed in pituitary endocrine cells, predominantly

in prolactin- and TSH-secreting cells. The study reported that blocking CTLA-4 expression in these pituitary endocrine cells with a specific mAb led to site-specific deposition of complement components, pituitary infiltration and antibody formation. The antibodies recognized predominantly TSH-secreting cells and, less frequently, FSH- or ACTH-secreting cells (Iwama *et al.* 2014).

Overall, hypophysitis is caused by a type II hypersensitivity reaction in which the CTLA-4 antibody binds to the cognate antigen expressed on pituitary cells, activates complement and promotes gland destruction (Laurent *et al.* 2013, Iwama *et al.* 2014, Kuehn *et al.* 2014, Schubert *et al.* 2014, Romano *et al.* 2015). Conversely, patients treated with PD-1 or PD-L1 IgG4 mAb, which are less effective for antibody-dependent cell-mediated cytotoxicity (ADCC), rarely develop pituitary damage (Garred *et al.* 1989, Michaelsen *et al.* 1991, Bruhns *et al.* 2009, Vidarsson *et al.* 2014, Rizvi *et al.* 2015a).

Anti-PD-1 and anti-PD-L1 mAbs

Hypophysitis with anti-PD-(L)1 mAbs is rarer than with anti-CTLA-4 antibodies. For example, in patients treated with nivolumab and pembrolizumab, only 0.6% developed hypophysitis, with a median time to onset of 4.2 months (range: 1.4–11 months) (Topalian *et al.* 2012, Robert *et al.* 2014, 2015b, Weber *et al.* 2015a, Ribas *et al.* 2016). For patients using durvalumab, a safety database that combined 1414 patients showed that only 1 patient (<0.1%) developed hypophysitis, with accompanying hypopituitarism, adrenal insufficiency and diabetes insipidus (Rizvi *et al.* 2015a). Similarly, in 523 patients who received atezolizumab for treatment of urothelial carcinoma, hypophysitis was found in 0.2% (1/523 urothelial carcinoma) (Rosenberg *et al.* 2016).

Hypophysitis was more frequently observed, similar to anti-CTLA-4 monotherapy (9%), when combination therapy with anti-CTLA-4 and anti-PD-L1 was used (Wolchok *et al.* 2013, Larkin *et al.* 2015, Postow *et al.* 2015).

Thyroid dysfunction

Distinguishing between primary or secondary dysfunction of the thyroid gland is of paramount importance. Secondary (central) hypothyroidism, with low or normal TSH and low free T_4 , is due to central dysfunction and should lead to the suspicion of hypophysitis induced by anti-CTLA-4 mAbs. Primary hypothyroidism, with

high TSH and normal or low free T_4 , is seen more with anti-PD-1 or anti-PD-L1 mAbs.

The incidence of thyroid dysfunction in patients treated with anti-PD-1 or anti-PD-L1 mAbs ranges from 4 to 19.5%, with a variable time to onset (Table 2). In the study by Reck and coworkers that investigated pembrolizumab in patients with NSCLC, the incidence of hyperthyroidism and hypothyroidism was 7.8 and 9.1%, respectively (Reck *et al.* 2016). In most studies, the majority of the cases are considered mild (grade 1 or 2) and resolution can be observed in 20–30% of patients with hypothyroidism and in up to 75% of patients with hyperthyroidism treated with nivolumab or pembrolizumab (Hamanishi *et al.* 2015, O'Donnell *et al.* 2015, Reck *et al.* 2016, El-Khoueiry *et al.* 2017).

The clinical manifestations of hypothyroidism include fatigue, weakness, asthenia, constipation, cold intolerance, dry skin and weight gain. Hyperthyroidism can be manifested as new-onset atrial fibrillation, diarrhea, heat intolerance, excessive diaphoresis and weight loss.

The spectrum of thyroid disturbances associated with immune checkpoint inhibitors include painless thyroiditis with transient thyrotoxicosis, transient or long-standing hypothyroidism, thyroid eye disease and occasionally severe forms of thyroid disease such as thyroid storm (Borodic *et al.* 2011, Hamnvik *et al.* 2011, Min *et al.* 2011, McElnea *et al.* 2014, Min & Hodi 2014, Carl *et al.* 2015, Orlov *et al.* 2015, Yu *et al.* 2015, Joshi *et al.* 2016). Rare cases of Graves' ophthalmopathy have been reported with elevation of TSH-receptor antibodies but normal thyroid function (Borodic *et al.* 2011, Min *et al.* 2011).

The mechanism responsible for immunotherapy-related thyroid dysfunction is still unclear. Orlov and coworkers reported 10 cases of painless thyroiditis syndrome following anti-PD1 therapy (Orlov *et al.* 2015). Six patients presented with an initial thyrotoxic phase from which 4 (67%) were positive for anti-thyroid peroxidase (anti-TPO) and positive for antithyroglobulin (anti-Tg), whereas all were negative for thyrotropin binding inhibitory immunoglobulins (TBII). Thyrotoxicosis resolved spontaneously in all patients and was followed by hypothyroidism. There were 4 patients who presented with hypothyroidism without previously detected thyrotoxic phase and had serological evidence of positive anti-Tg and anti-TPO antibodies (Orlov *et al.* 2015).

Anti-PD1 mAbs

The incidence of thyroid dysfunction with nivolumab is similar to pembrolizumab (Lu *et al.* 2015, Reck *et al.* 2016)

(Table 2). Hypothyroidism occurred in about 9% with a median time to onset of 2.9 months (1 day to 16.6 months). Resolution occurred in 35% of patients. The incidence of hypothyroidism with pembrolizumab, evaluated in more than 2800 patients, was 7–9.1%, mainly grade 2 (6.2%) with a median time to onset of 3.5 months (1 day to 18.9 months) (Table 2). Hypothyroidism resolved in about 20% of the patients. The incidence of new or worsening hypothyroidism was higher in patients with head and neck squamous cell carcinoma (HNSCC) than with urothelial carcinoma, occurring in 28 (15%) of 192 patients receiving pembrolizumab, including grade 3 (0.5%) hypothyroidism. This higher frequency is likely related to external radiotherapy to the neck which by itself is a risk factor for hypothyroidism.

Anti-PD-L1 mAbs

In patients who received avelumab, hypothyroidism occurred in 90/1738 (5%) patients and hyperthyroidism in 7 patients (0.4%). The median time to onset of thyroid dysfunction was 2.8 months (2 weeks to 13 months). Thyroid disease resolved in 7 (7%) of the 97 patients (Shitara *et al.* 2015, Yamada *et al.* 2015).

Across clinical trials for urothelial carcinoma and NSCLC with atezolizumab, hypothyroidism was found in 3.9% (77/1978) and hyperthyroidism in 1.0% (20/1978) (Rosenberg *et al.* 2016).

In the combined safety database using durvalumab, hypothyroidism occurred in 136/1414 (9.6%), hyperthyroidism occurred in 9/182 (4.9%), all were grade 1–2 and median time to first onset was 43 days (14–71 days). In another study, hyperthyroidism occurred in 81/1414 (5.7%) (Rizvi *et al.* 2015a).

Anti-CTLA4 mAbs

The incidence of thyroid dysfunction in patients treated with ipilimumab ranges from 1 to 8.9% (Ryder *et al.* 2014, Abdel-Rahman *et al.* 2016). The onset of anti-CTLA-4 thyroid dysfunction is variable, occurring after 2–4 infusions on average, but up to three years after the first infusion (Ryder *et al.* 2014). The male-to-female ratio of hypothyroidism was approximately 6:9. Most cases have a subclinical course or may be transient, but it can also evolve to permanent hypothyroidism with the need of thyroid hormone replacement. The administration of anti-CTLA-4 antibodies does not seem to worsen previous thyroid diseases. Hypophysitis and primary thyroid

dysfunction may be concurrent, especially in patients in use of ipilimumab and anti-PD-1 agents.

Much higher incidence of hyper and hypothyroidism occurred when combination therapy with anti-CTLA-4 and anti-PD-L1 was used (16 and 14%, respectively).

Other endocrine irAEs

Primary adrenal insufficiency

Primary adrenal insufficiency is rare. In patients using ipilimumab, 0.8–1.6% of the studied patients reported primary insufficiency after either monotherapy or combination with anti-PD-(L)1 therapy. With nivolumab, primary adrenal insufficiency occurred in 1% (20/1994) of the patients and median time to onset was 4.3 months (range: 15 days to 21 months). In patients treated with avelumab, primary adrenal insufficiency occurred in 8/1738 patients (0.5%), and only one patient (0.1%) had grade 3 adrenal insufficiency. The median time to onset of primary adrenal insufficiency for avelumab is 2.5 months (range: 1 day to 8 months). With atezolizumab, primary adrenal insufficiency occurred in 0.4% (7/1978), two with grade 3 and 5 with grade 1–2. In the combined safety database using durvalumab, the frequency of primary adrenal insufficiency was 0.9% (13/1414), being grade 3 in 0.1% (Table 2).

Despite the lack of clinically manifest hypoadrenalism, there have been recent reports of radiological evidence of adrenalitis, newly symmetrically and smoothly enlarged adrenal glands, with normal endocrine function following immune checkpoint therapy, consistent with a subclinical form of adrenalitis (Bacanovic *et al.* 2015).

Type 1 diabetes mellitus

Type 1 diabetes mellitus (DM) is not a frequent adverse event observed in patients treated with immunotherapy. It has not been reported with the use of ipilimumab alone so far. Type 1 DM occurred in 0.9% of patients treated with nivolumab and in 0.2% of patients treated with pembrolizumab. Diabetic ketoacidosis was reported in a few of these cases. The median time to onset was 4.4 months (range: 15 days to 22 months) (Robert *et al.* 2015a,b, Ribas *et al.* 2016). In patients who received avelumab, type 1 diabetes occurred in 0.1% (2/1738), all presented with grade 3 hyperglycemia. For atezolizumab, one patient with urothelial carcinoma and three patients with NSCLC of 1978 patients developed type 1 DM (Spira *et al.* 2015, Yamada *et al.* 2015). In the combined safety

database of durvalumab, type 1 DM occurred in only one (0.1%) patient (Hamid *et al.* 2013, Rizvi *et al.* 2015b, Shitara *et al.* 2015, Spira *et al.* 2015, Yamada *et al.* 2015).

Hypoparathyroidism

Recently, there was a report of a case of symptomatic hypocalcemia due to acute hypoparathyroidism in a patient using combination of nivolumab and ipilimumab (Win *et al.* 2017).

Diagnosis and treatment

Pituitary dysfunctions

Monitoring In addition to baseline pituitary function tests, regular monitoring of TSH and free T₄ is recommended monthly during treatment and should also be promptly ordered when suggesting symptoms of hypophysitis are present. When using anti-CTLA-4 agents, ACTH and cortisol levels should also be assessed routinely (Fig. 1).

Diagnosis In the suspicion of hypophysitis, a MRI should be performed to evaluate the pituitary and to exclude other causes of pituitary dysfunction such as brain metastases. A hormone profile assessment should be carried out, including TSH and free T₄, ACTH, cortisol, LH, FSH, prolactin, estradiol in females and testosterone in males. As diabetes insipidus is extremely rare, it should be investigated only in the presence of symptoms such as polyuria and polydipsia (Dillard *et al.* 2010). It is important to note that many metastatic patients receive corticosteroids, which impair evaluation of the pituitary–adrenal axis.

The diagnosis of hypophysitis is presumptive and is based on the presence of laboratory abnormalities suggestive of hypopituitarism and reversible pituitary enlargement seen at MRI, although since pituitary enlargement is transient and often mild, pituitary MRI may be normal especially if imaging is delayed. Severe fatigue, headache and myalgia should lead to the suspicion of hypophysitis and pituitary MRI should be promptly requested. Secondary adrenal insufficiency is confirmed by the presence of normal or low morning adrenocorticotrophic hormone (ACTH) and low or undetectable cortisol levels. The ACTH (cosyntropin) stimulation test can be performed; however, it is important to note that sensitivity can be lower with early secondary adrenal insufficiency as adrenal glands might maintain

response to ACTH in the acute phase of pituitary damage (Mitchell *et al.* 2009). In these cases, the low-dose ACTH stimulation test (1 µg) could be an option (Kazlauskaitė *et al.* 2008, Ospina *et al.* 2016).

Secondary hypothyroidism is diagnosed by the presence of normal or low thyroid-stimulating hormone (TSH) with low free thyroxine (FT₄) levels. To a lesser extent, secondary hypogonadism may also occur and the growth hormone axis is usually spared. Serum prolactin can be low, normal or high; the latter likely secondary to compression of the stalk.

Routine monitoring is critical as patients may be oligosymptomatic and symptoms may be vague, such as fatigue. Additionally, the use of exogenous glucocorticoids may mask the diagnosis of hypophysitis, so that a clinician must have a high index of suspicion, especially when glucocorticoids are tapered or weaned off to avoid adrenal crisis. Another possible confounding factor occurs with cancer patients undergoing chemotherapy, who can present with low TSH and central hypogonadism. These alterations may complicate initial assessment of thyrotroph and gonadotroph function following ipilimumab therapy. Figure 1 summarizes a suggested recommendation for biochemical evaluation and monitoring of pituitary dysfunction in patients treated with immunotherapy.

Treatment Glucocorticoid and thyroid hormone replacement should be introduced following a diagnosis of hypophysitis; steroid replacement should precede levothyroxine to avoid adrenal crisis. Testosterone replacement in men and estradiol replacement in selected premenopausal women should be considered. Growth hormone treatment is contraindicated. While some patients recover hormonal function, the use of concomitant treatments, such as glucocorticoid therapy and external beam radiotherapy, may impact recovery (Downey *et al.* 2007, Faje *et al.* 2014, Ryder *et al.* 2014). In fact, recovery of the adrenal axis is rare. In the subset of patients with improvement of the pituitary function what is observed is the recovery of the thyroidal and gonadal axis. The time to recovery has not been defined and hypopituitarism may persist in some patients indefinitely (Faje 2016).

Usually, immunotherapy can be maintained since pituitary hormones can safely be replaced. Cancer treatment should only be withheld, temporarily, in the rare occasions when there are symptoms related to mass effect of pituitary enlargement, such as vision loss and headache.

Figure 2

Suggested recommendation for biochemical evaluation and monitoring of thyroid dysfunction in patients treated with immunotherapy. *Thyroid antibodies: thyroid peroxidase and thyroglobulin antibodies. **Radioactive iodine and technetium uptake is inaccurate in face of recent use of iodine contrast-enhanced imaging. fT₄, free thyroxine; LT₄, levothyroxine; TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating immunoglobulin; tT₃, total triiodothyronine; US, ultrasound.

High-dose steroids (prednisolone 0.5–1 mg/kg/day or equivalent) is appropriate for patients with severe symptoms from hypopituitarism or from hypophysitis, including patients with severe hyponatremia from adrenal insufficiency and patients with headache and visual abnormalities from pituitary enlargement abutting the optic chiasm. Otherwise, patients with mild symptoms of hypophysitis and hypopituitarism can be treated with lower doses or physiologic doses of steroids (for example, 20–30 mg of hydrocortisone in split doses or an equivalent dose of prednisone) (Faje et al. 2014, Min et al. 2015).

In a subset of patients, pituitary function recovery may occur, mainly thyroidal and gonadal axis recovery. Adrenal axis recovery is rare. The time of function recovery is not well defined, and hypopituitarism may persist in some patients indefinitely (Faje 2016).

Thyroid dysfunction

Monitoring In addition to baseline thyroid function tests (TFT), regular monitoring of thyroid hormone levels (TSH and free T₄) is recommended before each treatment and also should be promptly accessed when suggesting symptoms are present (Fig. 2).

Diagnosis Persistently abnormal (particularly low) TSH levels, with low free T₄ may represent secondary hypothyroidism resulting from immunotherapy-induced hypophysitis. However, suppressed TSH levels may also occur due to high-dose steroids administered for other irAEs or brain metastases. Thus, in the appropriate clinical context, low TSH levels with normal or low FT₄ levels should prompt evaluation, if not already performed, of the pituitary–adrenal axis with a morning ACTH and cortisol level.

In thyroiditis, primary hypothyroidism (high TSH and/or low free T₄) might be preceded by a transient hyperthyroidism (low TSH, elevated free T₄ and/or T₃). Thyroid antibodies, antithyroglobulin and anti-thyroid peroxidase (TPO), should be measured when a primary thyroid dysfunction is suspected.

Treatment Asymptomatic patients with mildly elevated TSH (<10 U/L) usually can be only observed. If required, thyroid hormone therapy should be initiated as an initial full replacement or as partial replacement with gradual increments in the dose titrated upward using serum TSH as the goal. Dose adjustments should be made with TSH assessment 4–6 weeks after any dosage

change. In the absence of other immunotherapy-induced endocrine dysfunction, patients do not require treatment with glucocorticoid.

Thyroiditis with transient thyrotoxicosis can be managed symptomatically with β -blockers. Anti-thyroid drugs are rarely needed and are indicated to patients with thyroid hormone overproduction such as in Graves' disease. To distinguish between thyroiditis and Graves' disease, a thyroid scan with uptake could be performed. However, the use of iodine contrast-enhanced imaging in oncological patients frequently precludes its use. An alternative, when expertise is available, is ultrasonography with color flow Doppler where increased flow suggests thyroid hyperactivity while hypovascularity suggests destructive thyroiditis. Immunoassays to detect thyroid-stimulating immunoglobulin, TPO and thyroglobulin antibodies can be helpful in this setting. Those patients with mild symptoms of hyperthyroidism from thyroiditis can be observed and monitored for symptom progression, as well as for the development of permanent hypothyroidism.

Immunotherapy can be maintained, unless in case of severe thyrotoxicosis when the drug might be paused until symptoms improve.

Primary adrenal insufficiency

Diagnosis Primary adrenal insufficiency associated with adrenal crisis is exceedingly rare (Hodi *et al.* 2010, Brahmer *et al.* 2012, Corsello *et al.* 2013, Hamid *et al.* 2013). It may be diagnosed by the presence of volume depletion, electrolyte disturbances, eosinophilia and low or suppressed morning serum cortisol with high ACTH levels. Immunotherapy usually can be maintained.

Adrenal crisis is the most life-threatening endocrinopathy requiring prompt diagnosis and treatment. Adrenal crisis usually presents as hypovolemic shock, associated with nonspecific symptoms such as nausea, vomiting, fatigue, lethargy, confusion or coma. If suspected, serum cortisol and ACTH should be obtained and treatment should be initiated immediately thereafter, without waiting for results. Treatment consists of intravenous hydrocortisone, 100mg every 6–8h in addition to aggressive fluid replacement. Endocrinology consultation is highly recommended.

Autoimmune diabetes

Type 1 DM may rarely occur and when present, ketoacidosis must be investigated and treated, mainly if

serum glucose is greater than 250mg/dL (Kitabchi *et al.* 2009). Appropriate treatment with basal-bolus insulin is recommended. Anti-GAD65 can be performed to confirm the autoimmunity.

Conclusion

Given the breadth of the emerging immunotherapy field, clinicians should be aware of the unique set of drug-related adverse effects, now known as immune-related adverse events (irAE). Predicting and understanding the aforementioned toxicity will require better reporting of these toxicities, as well as more translational research.

With regards to endocrine disorders, hypophysitis and thyroid dysfunction are the most common abnormalities. For patients on anti-CTLA-4 treatment, the pituitary hormone profile should be appropriately monitored throughout immunotherapy and treatment should be instituted as soon as central adrenal insufficiency and/or central hypothyroidism is diagnosed.

Primary thyroid dysfunction is more frequently observed in patients treated with anti-PD1 and anti-PD-L1 antibodies. Both primary hypothyroidism and hyperthyroidism can occur. Hyperthyroidism can be transient, but followed by hypothyroidism, which may require lifelong treatment.

Endocrine side effects should be promptly diagnosed and treated as they result in reduced quality of life and reduced tolerance to immunotherapy. As in most cases, endocrine side effects can be adequately managed, and they do not contraindicate the continued use of immunotherapy.

Physicians should be aware that autoimmune endocrine disorders can occur during and long after immunotherapy and a multidisciplinary approach is strongly recommended. In addition, patient education regarding irAEs is of utmost importance so that notification of symptoms prompts early diagnosis and treatment.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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