

Endocrine Side Effects Induced by Immune Checkpoint Inhibitors

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Context: In recent years, progress has been made in cancer immunotherapy by the development of drugs acting as modulators of immune checkpoint proteins, such as the cytotoxic T-lymphocyte antigen-4 (CTLA4) and programmed death-1 (PD-1), two co-inhibitory receptors that are expressed on T cells upon activation. These molecules play crucial roles in maintaining immune homeostasis by down-regulating T-cell signaling, thereby preventing unbridled T-cell proliferation while maintaining tolerance to self-antigens, such as tumor-associated antigens. CTLA4 blockade through systemic administration of the CTLA4-blocking antibody ipilimumab was shown to confer significant survival benefit and prolonged stable disease in patients affected by advanced cutaneous melanoma. Other immune checkpoint inhibitors are under clinical evaluation. However, immune checkpoint blockade can lead to the breaking of immune self-tolerance, thereby inducing a novel syndrome of autoimmune/autoinflammatory side effects, designated as “immune-related adverse events,” mainly including rash, colitis, hepatitis, and endocrinopathies.

Data Acquisition: We searched the medical literature using the words “hypophysitis,” “hypopituitarism,” “thyroid,” “adrenal insufficiency,” and “endocrine adverse events” in association with “immune checkpoint inhibitors,” “ipilimumab,” “tremelimumab,” “PD-1,” and “PD-1-L.”

Evidence Synthesis: The spectrum of endocrine disease experienced by patients treated with ipilimumab includes most commonly hypophysitis, more rarely thyroid disease or abnormalities in thyroid function tests, and occasionally primary adrenal insufficiency. Hypophysitis has emerged as a distinctive side effect of CTLA4-blocking antibodies, establishing a new form of autoimmune pituitary disease. This condition, if not promptly recognized, may be life-threatening (due to secondary hypoadrenalism). Hypopituitarism caused by these agents is rarely reversible, and prolonged or lifelong substitutive hormonal treatment is often required. The precise mechanism of injury to the endocrine system triggered by these drugs is yet to be fully elucidated.

Conclusions: Although reports of endocrine side effects caused by cancer immune therapy are abundant, their exact prevalence and mechanism are unclear. Well-designed correlative studies oriented to finding and validating predictive factors of autoimmune toxicity are urgently needed. (*J Clin Endocrinol Metab* 98: 1361–1375, 2013)

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Abbreviations: aCM, advanced cutaneous melanoma; anti-CTLA4-mAbs, anti-CTLA4 mAbs; anti-CTLA4-H, hypophysitis induced by anti-CTLA4-mAbs; anti-CTLA4-T, thyrotoxicosis induced by anti-CTLA4-mAbs; AE, adverse event; CTLA4, cytotoxic T-lymphocyte antigen-4; E-IRAE, endocrine immune-related adverse event; mAb, monoclonal antibody; mCRPC, metastatic castration-resistant prostate cancer; MHC, major histocompatibility complex; MRI, magnetic resonance imaging; PAI, primary adrenal insufficiency; PD-1, programmed death-1; PD-1-L, PD-1 ligand; PSA, prostate-specific antigen; RCC, renal cell cancer; T-regs, T-regulatory cells.

The appearance of cancer reveals that the host immunity failed to control tumor progression due to ineffectiveness or to acquired tolerance (1). Several mechanisms are proposed to explain cancer immune escape, including the presence of immunoregulatory cell types and the production of immunosuppressive factors by leukocytes or by cancer cells themselves (2). Anticancer immunotherapy aims to improve the ability to immunologically reject the tumor by generating an adequate immune response, breaking tumor-induced immune tolerance. To attain these goals, several approaches have been developed, including immunization with cancer cells or molecules and adoptive T-cell transfer (3). The administration of immunostimulatory agents such as interferons and IL-2, which induce a less specific activation of the immune system, can be effective in few hematological malignancies, with less marked efficacy in solid tumors (ie, melanoma and renal cell cancer [RCC]) (3). Current research has led to the development of immune regulatory antibodies that inhibit immunological checkpoints, such as the cytotoxic T-lymphocyte antigen-4 receptor (CTLA4), the programmed death-1 (PD-1) receptor pathway, and others (4). These agents enhance immunological antitumor activity by breaking down tumor immune tolerance (5, 6). Particularly, a new class of immunomodulating antibodies directed against CTLA4 (anti-CTLA4-mAbs) has been extensively tested in clinical trials (7). One of these agents, ipilimumab, demonstrated for the first time improvement of overall survival in advanced cutaneous melanoma (aCM) and was found to be active against other tumor types (7, 8). However, inhibition of CTLA4 induces side effects defined as “immune-related adverse events” (IRAEs) (9). Autoimmunity is the suggested mechanism sustaining these toxicities (10, 11). IRAEs mainly include colitis/diarrhea, dermatitis, hepatitis, and endocrinopathies (12). Among endocrine toxicities, hypophysitis has emerged as a distinctive side effect (9, 13). This condition, because of secondary adrenal insufficiency, may be life-threatening if not promptly recognized (14). Monoclonal antibodies (mAbs) blocking PD-1 or one of its ligands (PD-1-L) are at an earlier phase of clinical development (6, 15). Endocrine toxicity has been reported with these agents as well.

Herein, we analyze in parallel the available findings that characterize “classic” and anti-CTLA4-induced hypophysitis, highlighting common features and some differences. In addition, clinical and pathogenic aspects of the other endocrine IRAEs (E-IRAEs) are scrutinized.

Endocrine Toxicities Induced by Anti-CTLA4 mAbs

Ipilimumab and tremelimumab are mAbs directed against CTLA4, a receptor expressed on T cells that exerts a sup-

pressive effect on the immune response after T-cell/antigen-presenting cell interaction (5, 16). Blocking the receptor, an increased T-cell activation and antitumor effects are obtained (17). In 2 large phase III trials, ipilimumab was shown to confer significant survival benefit and prolonged stable disease in patients affected by aCM (8, 18). Similar results were not obtained by tremelimumab (19). In 2011, the US Food and Drug Administration and the European Medicines Agency licensed ipilimumab for advanced melanoma (20, 21). The approved dose is 3 mg/kg administered as an iv infusion every 3 weeks for a total of 4 doses. In some patients, maintenance therapy may continue with additional infusions at longer intervals. In clinical trials, the dose ranged from 0.3 to 10 mg/kg. Objective clinical responses and an overall survival benefit were demonstrated with 3 mg/kg (8, 22), but not with the lowest dose. The toxicity profile worsens in a dose-dependent manner. In a pooled analysis of 325 patients treated with 10 mg/kg ipilimumab every 3 weeks for 4 doses, IRAEs of any grade (G) were observed in 72.3%. G3–4 IRAEs were observed in 25.2%, mainly in the gastrointestinal tract (12%), liver (7%), skin (3%), and endocrine system (3%) (23). Anti-CTLA4-IRAEs are managed through adherence to specific guidelines (24–26), including the administration of systemic glucocorticoids or other immunosuppressants. Retrospective analysis suggests that patients who experience G3–4 IRAEs may be more likely to benefit from anti-CTLA4 therapy (9, 10, 27).

The spectrum of E-IRAEs includes hypopituitarism caused by hypophysitis and, more rarely, thyroid disease or abnormalities in thyroid function tests. Primary adrenal insufficiency (PAI) has been reported occasionally as well (for toxicity grading, see Table 1).

Hypophysitis induced by anti-CTLA4-mAbs

In initial trials, the incidence of hypophysitis induced by anti-CTLA4-mAbs (anti-CTLA4-H) varied considerably (0–17%) (13). In more recent larger trials, the incidence seemed not to exceed 5% (Table 2). Although most data are from patients affected by aCM, anti-CTLA4-H has been reported in patients with different tumor types.

The incidence of anti-CTLA4-H seems to be dose-dependent (Table 2). At the lower ipilimumab dose (1–3 mg/kg), it occurred in 1.8–3.3% of cases (10, 11). Only in 1 study (28) of 139 melanoma patients receiving 1–3 mg/kg \pm a peptide vaccine, G3–4 hypophysitis was diagnosed in 9% of patients. When the dose exceeds 3 mg/kg, hypophysitis varies from 4.9 to 17% (29, 30). In a recent phase I dose-escalation trial, 30 patients with metastatic castration-resistant prostate cancer (mCRPC) received ipilimumab (1–10 mg/kg) in combination with an anti-prostate-specific antigen (PSA) vaccine. Hypophysitis oc-

Table 1. Toxicity Grading of Endocrine Adverse Events Associated to Administration of Immune Checkpoint Inhibitors, Such as Hypothyroidism, Hyperthyroidism, Adrenal Insufficiency, Hypophysitis, According to Common Terminology Criteria for Adverse Events (CTCAE) of National Institutes of Health – National Cancer Institute (95)

Endocrine Adverse Event	Grade	Description
Hypothyroidism	1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
	2	Symptomatic; thyroid replacement indicated; limiting instrumental activity of daily living (ADL)
	3	Severe symptoms; limiting self care ADL; hospitalization indicated
	4	Life-threatening consequences; urgent intervention indicated
	5	Death
Hyperthyroidism	1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
	2	Symptomatic; thyroid suppression therapy indicated; limiting instrumental activity of daily living (ADL)
	3	Severe symptoms; limiting self care ADL; hospitalization indicated
	4	Life-threatening consequences; urgent intervention indicated
	5	Death
Adrenal insufficiency	1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
	2	Moderate symptoms; medical intervention indicated
	3	Severe symptoms; hospitalization indicated
	4	Life-threatening consequences; urgent intervention indicated
	5	Death
Hypophysitis	1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
	2	Moderate; minimal, local or noninvasive; intervention indicated; limiting age-appropriate instrumental ADL
	3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL
	4	Life-threatening consequences; urgent intervention indicated
	5	Death

Hypothyroidism is defined as a disorder characterized by a decrease in production of thyroid hormone by the thyroid gland. Hyperthyroidism is defined as a disorder characterized by an excessive levels of thyroid hormone in the body. Adrenal insufficiency is defined as a disorder that occurs when the adrenal cortex does not produce enough of the hormone cortisol and in some cases, the hormone aldosterone. It may be due to a disorder of the adrenal cortex as in Addison's disease or primary adrenal insufficiency. General toxicity grading for endocrine adverse event is applicable to hypophysitis. No specific definition of hypophysitis is available yet.

curred in 4 (13.3%) patients with higher doses (5 mg/kg, 2 patients G2; 10 mg/kg, 1 patient G2 and 1 patient G3) (31). In another study of mCRPC evaluating the combination of ipilimumab (0.3 to 5 mg/kg) with prostate cancer cell vaccine, G2–3 hypophysitis was diagnosed in all 3 patients at the third dose level (3 mg/kg), in 2 of 16 (13%) patients of the 3 mg/kg expansion cohort, and in 2 of 3 patients at the higher dose (5 mg/kg) (32). Higher rates of hypophysitis (14%) are associated with the administration of ipilimumab in combination with bevacizumab, an agent with antiangiogenic and putative immunogenic activities (33).

The 10 mg/kg ipilimumab dose was not associated with hypophysitis when combined with chemotherapy in all studies (18, 34, 35) but one (36). Similarly, hypophysitis was not reported in 72 patients affected by aCM with brain radiotherapy-pretreated metastases (37). These data suggest that cytotoxic chemotherapy and radiotherapy may prevent anti-CTLA4-H, presum-

ably through immune cell depletion. Tremelimumab has been reported to induce hypophysitis in 0–2.5% of patients (Table 2).

Patients with anti-CTLA4-H were almost all male. They present with nonspecific symptoms such as fatigue, weakness, headache, nausea, vertigo, behavior change, visual impairments such as diplopia (less frequent than in classic lymphocytic autoimmune hypophysitis [LAH]), confusion, memory loss, loss of libido (29, 38), anorexia, insomnia, hallucinations, temperature intolerance, and subjective sensation of fever and chills (39).

The onset of anti-CTLA4-H symptoms occurs at an average of 6–12 weeks after initiation of therapy. Patients who received 3 mg/kg ipilimumab developed symptoms at a median time of 11 weeks (ie, before the fourth dose), suggesting a possible cumulative effect (40). In a trial of mCRPC (10 mg/kg), hypophysitis symptoms occurred after the first infusion (4 wk) in 1 patient and after the fourth (16 wk) in another (39).

Table 2. The Incidence of Endocrine Adverse Events in Studies on New Immunoregulatory Anticancer Agents

Anticancer Agent	Authors	Phase	Cancer(s) (No. of Patients)	Schedule of Treatment	Incidence of Endocrine Adverse Events (All Grade)	Incidence of Other IRAEs (G3–4)
Ipilimumab	Attia et al (10)	I	Pretreated stage IV melanoma (56 pts)	3 mg/kg every 3 weeks, or 3 mg/kg → doses reduced to 1 mg/kg every 3 weeks + vaccination with modified HLA-A*0201-restricted peptides from gp100 MAA	G3–4 hypophysitis: 1 pt (1.8%)	G3–4 colitis: 7 pts (13%), dermatitis: 4 pts (7%), uveitis: 1 pt (1.8%), enterocolitis: 1 pt (1.8%), hepatitis: 1 pt (1.8%)
	Maker et al (44)	I	Naïve-metastatic melanoma (36 pts)	1–3 mg/kg + interleukin-2	No endocrine toxicity was reported	G3–4 colitis: 4 pts (11%), uveitis: 1 pt (2.8%), arthritis: 1 pt (2.8%)
	Maker et al (30)	I-II	Pretreated stage IV melanoma (46 pts)	3 → 9 mg/kg (intra-patient dose escalation)	G3–4 hypophysitis: 8 pts (17%); (5 mg/kg: 1 pt), (9 mg/kg: 7 pts) G3–4 hypothyroidism: 1 pt (2.2%)	G3–4 colitis/diarrhoea: 6 pts (13%), uveitis: 1 pt (2.8%), arthritis: 1 pt (2.8%), dermatitis: 1 pt (2.8%), hepatitis: 1 pt (2.8%), nephritis: 1 pt (2.8%)
	Downey et al (28)	I-II	Pretreated stage IV melanoma (139 pts)	3 mg/kg + peptide vaccinations or intra-patient dose escalation → peptides (HLA-A*0201status)	G3–4 hypophysitis: 13 pts (9%) G1–2 hypothyroidism: 3 pts (2%)	G3–4 enterocolitis: 24 pts (17%), dermatitis: 8 pts (6%), hepatitis: 2 pts (3%), uveitis: 3 pts (2%)
	Phan et al (43)	II	Pretreated stage IV melanoma (14 pts)	3 mg/kg + peptide vaccinations (two modified HLA-A*0201-restricted peptides from gp100)	G3/4 hypophysitis: 1 pt (7.1%)	G3–4 dermatitis: 3 pts (21.4%), enterocolitis/colitis: 2 pts (14.3%), hepatitis: 1 pt (7.1%)
	Blansfield et al (29)	R.S.	Pretreated stage IV melanoma (113 pts) and RCC (50 pts)	3 mg/kg every 3 weeks	G3–4 hypophysitis: 8/163 pts (4.9%), 6/113 melanoma pts (5%), 2/50 RCC pts (4%) G2–3 hypopituitarism: 1 pt (3.7%)	NR. The report focused on clinical aspects of patients who developed anti-CTLA4-IH
	Royal et al (96)	II	Metastatic pancreas ADC (27 pts)	3 mg/kg every 3 weeks × 4 for a maximum 2 courses.	G2–3 hypopituitarism (DLT): 1 pt (4%)	G3–4 colitis: 1 pt (3.7%); encephalitis: 1 pt (3.7%)
	Weber et al (97)	I	Stages IIIc/IV melanoma (25 pts)	3 mg/kg every 8 weeks for 12 months + MART-1/gp100/tyrosinase peptides	No endocrine toxicity was reported	No G4 toxicity; G2–3 DLT were GI toxicity: 2 (8%) and skin toxicity: 2 (8%)
	Fong et al (98)	I	mHRPC (18 pts)	Escalating doses (0.5, 1.5, 3 mg/kg) every 3 weeks for 4 cycles + GM-CSF	No endocrine toxicity was reported	No G4 toxicity; G3 skin (DLT)
	Small et al (99)	I	mPC (14 pts)	3 mg/kg single dose	No endocrine toxicity was reported	G3–4 asthenia: 1 pt (7.1%), pain: 1 pt (7.1%), rash: 1 pt (7.1%)
	Yang et al (11)	I	mRCC (61 pts)	3 mg/kg → 1 mg/kg or all doses at 3 mg/kg q 3 weeks G3–4 primary adrenal insufficiency: 1 pt (1.6%)	G3–4 hypopituitarism: 2 pts (3.3%)	(All doses) G3–4 enteritis/colitis: 17 pts (28%), skin: 1 pt (1.6%), arthralgia: 1 pt (1.6%), aseptic meningitis: 1 pt (1.6%)
	Weber et al (52)	I-II	Unresectable stage III or IV melanoma (88 pts)	Ipilimumab transfectoma -derived 2.8 mg/kg or 5 mg/kg for 3 doses, or ipilimumab hybridoma -derived 3 mg/kg for 3 doses	G3–4 adrenal insufficiency: 1 pt (1.2%)	(All doses) G3–4 colitis: 3 pts (3.4%), diarrhoea: 4 pts (45%), GI perforation: 1 pt (1.1%)
	Ansell et al (100)	I	Relapsed/Refractory B-Cell NHL (18 pts)	3 mg/kg → monthly 1 mg/kg × 3 months (dose level 1), → escalation to 3 mg/kg monthly × 4 months (dose level 2)	G1–2 hypophysitis: 1 pt (6%)	No G4 toxicity; G3 diarrhoea: 5 pts (28%), fatigue: 1 pt (6%), neutropenia: 1 pt (6%)

(Continued)

In most cases, magnetic resonance imaging (MRI) reveals enlargement of the pituitary gland (up to 60–100% of baseline size), with thickening of the stalk (29). The height of the gland in the sagittal view increases from 3.4–6 to 7.7–11.8 mm (29, 41). In some cases, the MRI is normal. The pituitary gland may enhance homogeneously or appear heterogeneous. In general, MRI changes appear to be of lesser magnitude than sporadic LAH (40). At follow-up, pituitary decreases gradually on glucocorticoid treatment in a variable period of time (4–12 wk), despite

a more rapid reduction of symptoms (40, 42, 43). Levels of ACTH, cortisol, TSH and free T₄, GH, prolactin, IGF-I, FSH, LH, and testosterone (in males) were variably altered, indicating different degrees of hypopituitarism (44). In anti-CTLA4-H, ACTH and TSH seem to be invariably lost (29, 39, 40). Most male patients (83–87%) had hypogonadotropic hypogonadism. Some of these findings may be confounded by sickness-induced hypogonadism and sick euthyroid syndrome. In a case series (42), 3 of 5 patients had low serum IGF-I. Pro-

Table 2. Continued

Anticancer Agent	Authors	Phase	Cancer(s) (No. of Patients)	Schedule of Treatment	Incidence of Endocrine Adverse Events (All Grade)	Incidence of Other IRAEs (G3–4)
	Hodi et al (8)	III	Pretreated unresectable stage III/IV melanoma (676 pts)	3 mg/kg every 3 weeks for 4 doses with or without gp100 vs. gp100 alone	Hypophysitis: G3, 2 pts (1.5%) in ipilimumab arm; G3, 2 pts (0.5%) in combination arm; 0 in gp100 arm Hypopituitarism: G3–4, 2 pts (1.6%); G1/2, 1 pt in ipilimumab arm; G3, 2 pts (0.8%); G1–2, 1 pt in the combination arm G1–2 hypothyroidism: 2 pts (1.5%) in ipilimumab arm, G3, 1 pt (0.3%); G1/2, 5 pts (1.6%) in the combined arm; G1/2, 2 pts (1.5%) in gp100 arm Adrenal insufficiency: G1–2, 2 pts (1.5%) in ipilimumab arm; G3, 2 pts (0.5%); G1–2 1 pt (0.3) in the combination arm	G3–4 diarrhea: 30.3%–27.5%; nausea, 39.9%–35.1%; vomiting, 19.7%–23.7%; abdominal pain, 17.6%–15.3%; colitis, 5.3%–7.6%; constipation, 21.3%–20.6%; pruritus/rash, 17.8%–24.4%; hepatic, 2.1%–3.8%; fatigue, 36.1%–42%; pyrexia, 20.5%–12.2%; headache, 17.1%–14.5%
	Hersh et al (53)	II	Chemotherapy-naïve pts with unresectable stage III/IV melanoma (72 pts)	3 mg/kg q 4 weeks for 4 doses ± DTIC (up to 6 cycles; 250 mg/m ² /day × 5 days)	G2 adrenal insufficiency: 1 pt (1.4%) (in ipilimumab + DTIC arm)	G3–4 colitis/diarrhoea: 2 pts (2.8%), GI hemorrhage: 2 pts (2.8%), vasculitis: 2 pts (2.8%), transaminitis: 2 pts (2.8%), skin: 2 pts (2.8%), multi-organ failure: 2 pts (2.8%)
	Wolchok et al (101)	II	Pretreated unresectable stage III/IV melanoma (217 pts)	0.3; 3; 10 mg/kg q 3 weeks for 4 cycles (induction) → q 3 months (maintenance).	E-IRAEs were globally reported Grade 3–4: 0.3 mg/kg: 0 pts; 3 mg/kg: 2 pts (1%); 10 mg/kg: 1 pt (0.5%) In the 3 mg/kg group, hypopituitarism lead to treatment withdrawal	G3–4 GI events 10 mg/kg: 11 pts (5%); 3 mg/kg: 2 pts (1%); 0.3 mg/kg: 0 pts. Liver: 10 mg/kg: 2 pts (1%). 3 mg/kg: 3 pts (1.4%); 0.3 mg/kg: 1 pt (0.5%). Others: 2 pts (1%)
	Hodi et al (33)	I	Unresectable stage III/IV melanoma (naïve/not) (21 pts)	10 mg/kg q 3 weeks × 4 → q 3 months + bevacizumab 7.5 mg/kg (Cohort 1) or 15 mg/kg (cohort 2) q 3 weeks.	Hypophysitis (grade not specified): 3 pts (14%) Thyroiditis (grade not specified): 4 pts (19%)	G3–4 hepatitis: 2 pts (9.5%), bilateral uveitis: 2 pts (9.5%); giant arteritis: 1 pt (4.8%) G2 colitis: 2 pts (9.5%)
	O'Day et al (102)	II	Pre-treated, unresectable stage III/IV melanoma (155 pts)	10 mg/kg q 3 weeks for 4 cycles (induction) → q 3 months (maintenance).	E-IRAEs were globally reported G3: 2 pts (1.3%); G4: 0 pts	G3–4 skin: 5 pts (3.2%), GI: 13 pts (8.4%), liver: 11 pts (7.1%), others: 4 pts (2.6%)
	Ku et al (103)	II	Refractory melanoma (compassionate use; 53 pts)	10 mg/kg q 3 weeks for 4 doses → every 12 weeks in case of CB	G2–3 hypophysitis with adrenal insufficiency: 2 pts (4%) G2 hypothyroidism: 1 pt (2%)	G3–4 diarrhoea: 17 pts (33%), colitis: 5 pts (10%), hepatitis: 4 pts (8%), pancreatitis: 1 pt (2%)

(Continued)

Table 2. Continued

Anticancer Agent	Authors	Phase	Cancer(s) (No. of Patients)	Schedule of Treatment	Incidence of Endocrine Adverse Events (All Grade)	Incidence of Other IRAEs (G3–4)
	Di Giacomo et al (51)	II	Pretreated unresectable stage III/IV melanoma (EAP: 27 pts)	10 mg/kg q 3 weeks for 4 doses → every 12 weeks in case of CB	G1–2 hypothyroidism: 2 pt (7.4%)	G3 diarrhoea: 2 pts (7.4%), transaminitis: 1 pt (3.7%), G4 pancytopenia: 1 pt (3.7%)
	Robert et al (18)	III	Untreated unresectable stage III/IV melanoma	10 mg/kg + dacarbazine (arm A) or dacarbazine + placebo (Arm B) (at weeks 1, 4, 7, and 10) → dacarbazine alone q 3 weeks through week 22 → ipilimumab or placebo q 12 weeks thereafter (maintenance therapy)	No endocrine toxicity was reported	Arm A: G4 ↑ transaminases: 23 pts (9.3%); G3 hepatitis/↑ transaminases: 74 pts (30%); G3 diarrhea: 14 pts (5.6%)
	Margolin et al (37)	II	Melanoma brain metastases (72 patient)	10 mg/kg q 3 weeks for 4 doses	No endocrine toxicity was reported	No G4 toxicity reported. G3 diarrhoea: 6 pts (12%); Rash: 1 pt (5%); ↑ transaminases 2 pts (10%)
	Madan et al (31)	I	Chemotherapy refractory/naïve mHRPC patients (30 pts)	1–10 mg/kg escalating dose + PSA-Tricom vaccine	Panhypophysitis: 4 pts (13.3%) (5 mg/kg: G2, 2 pts; 10 mg/kg: G3, 1 pt, G2, 1 pt) Hypothyroidism: 4 pts (13.3%) (5 mg/kg: G2, 2 pts; 10 mg/kg: G2, 2 pts); Adrenal insufficiency: 3 pts (10%) (5 mg/kg: G3, 1 pt; 10 mg/kg: G3, 1 pt; G2, 1 pt)	G3–4 diarrhoea or colitis: 3 mg/kg: G3, 1 pt; 5 mg/kg: G3, 1 pt; 10 mg/kg: G3, 1 pt, G4, 1 pt Rash: 10 mg/kg: G3, 2 pts Hepatic (↑ transaminases): 10 mg/kg: G3, 2 pts; Neutropenia: 3 mg/kg: G4, 1 pt
	DiGiacomo et al (35)	II	Unresectable stage III/IV melanoma (pretr./naïve) 86 pts	induction treatment: 10 mg/kg q 3 weeks for 4 doses + fotoemustine 100 mg/m ² i.v. weekly for 3 weeks and then q 3 weeks; pts with CR: maintenance treatment from week 24: ipilimumab q 12 weeks + fotemustine q 3 weeks	G1–2 thyroiditis: 2 pts (2%)	Myelotoxicity: 37 pts (43%); hepatic (↑ transaminases): 21 pts (24%); amylase/lipase increase: 5 pts (6%); colitis/diarrhoea: 4 pts (5%)
	Lynch et al (36)	IIb	NSCLC (stage III/IV; 204 pts)	Paclitaxel 175 mg/m ² + carboplatin (AUC 6) ± placebo/ipilimumab	G3 hypophysitis/hypopituitarism: 1 pt (0.5%) in the concurrent ipilimumab arm	Overall G3–4 IRAEs in ipilimumab arms: diarrhoea, 12 pts (5.9%); rash: 6 pts (2.9%); ↑ transaminases 4 pts (2%); hematology toxicity: 32 pts (15.8%)
	Reck et al (34)	II	Naïve ED- SCLC (130 pts)	Paclitaxel 175 mg/m + carboplatin (AUC 6) ± placebo/ipilimumab 10 mg/kg	No endocrine toxicity was reported	Overall G3–4 IRAEs in ipilimumab arms: diarrhoea, 14 pts (10.8%); rash: 5 pts (3.8%); ↑ transaminases 42 pts (32%); hematology toxicity: 43 pts (33%)
	Hamid O et al (104)	II	Pre-treated, unresectable stage III/IV melanoma (EAP; 830 pts)	10 mg/kg i.v. q 3 weeks up to 4 doses (induction) → 10 mg/kg q 12 weeks (maintenance)	Endocrinopathies: 4%	Any grade SAEs. Diarrhoea: 10%; colitis: 8%; dermatitis: 0.8%; hepatitis: 0.24%; intestinal perforations: 3 pts (0.36%); multi-organ failure: 1 pt (0.12%); acute respiratory distress syndrome: 1 pt (0.12%)
	van den Eertwegh et al (32)	I	CT-naïve mCRPC patients (28 pts)	0.3, 1, 3, 5 mg/kg escalating dose + GVAX	Hypophysitis: G2, 1 pt (3.6%); G3, 2 pt (7.1%) at 3.0 mg/kg dose level; G2, 2 pts (7.1%); G3, 2 pts (7.1%) at the 5.0 mg/kg dose level	At 5.0 mg/kg dose level: G4 sarcoid alveolitis 1 pt (3.6%) (DLT); G3 hepatitis, 1 pt (3.6%)

(Continued)

Table 2. Continued

Anticancer Agent	Authors	Phase	Cancer(s) (No. of Patients)	Schedule of Treatment	Incidence of Endocrine Adverse Events (All Grade)	Incidence of Other IRAEs (G3–4)
Tremelimumab	Ribas et al (105)	I	Metastatic malignancies (39 pts) (melanoma, n = 34; RCC, n = 4; CRC, n = 1)	0.01–15 mg/kg every 90 days	G2 hypopituitarism: 1 pt (2.5%) (15 mg/kg) G1 hypothyroidism: 1 pt (2.5%) G1 hyperthyroidism: 1 pt (2.5%) (15 mg/kg)	10 mg/kg: G3 asthma: 1 pt (2.5%); G3 diarrhoea: 1 pt (2.5%) 15 mg/kg: G3 diarrhoea: 2 pts (5%); G3 dermatitis: 1 pt (2.5%); G3 ↑ lipase: 1 pt (2.5%)
	Camacho et al (106)	I/II	Pre-treated unresectable stage III/IV melanoma (Phase I: 28 pts)(Phase II: 89 pts)	Phase I: 3, 6, 10 mg/kg Phase II: 10 mg/kg monthly 15 mg/kg IV every 90 days	Thyroiditis-hypothyroidism: 1 pt (10 mg/kg)	DLTs: hepatitis: 2 pts; edema & cellulitis: 1 pt; vasculitis, pruritus, skin exfoliation, rash: 1 pt G3–4 AEs (diarrhoea, rash, pruritus, fatigue, and nausea): 13% (10 mg/kg); 27% (15 mg/kg). SAEs: 9% (15 mg/kg); 23% (10 mg/kg). G3 diarrhoea: 21% (10 mg/kg), 9% (15 mg/kg)
	Ralph et al (107)	II	Pre-treated metastatic gastric and esophageal ADC (18 pts)	15 mg/kg IV every 90 days	No endocrine toxicity was reported	G3 diarrhoea, perforation and death: 1 pt; G3 transaminitis: 1 pt. Only 1 pt received 2 cycles of the study drug
	Kirkwood et al (50)	II	Refractory or relapsed advanced melanoma (251 pts)	15 mg/kg IV every 90 days	G3–4 hypophysitis: 1 pt (0.4%) Thyroid disorders: 8 pts (3.2%)	G3–4 diarrhoea: 28 pts (11%), fatigue: 6 pts (2%), colitis: 9 pts (4%) Treatment-related deaths: 2 pts (0.8%)
Chung et al (107)	II	Pretreated CT-insensitive or refractory mCRC (47 pts)	15 mg/kg IV every 90 days	G2 hypothyroidism: 1 pt (2%)	G3–4 diarrhoea: 5 pts (11%), colitis: 1 pt (2%), fatigue: 1 pt (2%) ↓ platelets: 1 pt (2%), hypokalemia: 1 pt (2%)	
Ribas et al (19)	III	Naïve, stage IV/unresectable stage IIIc melanoma (655 pts)	15 mg/kg IV every 90 days ± CT	Pituitary or adrenal gland: 3% Thyroid: 4%	G3–4 diarrhoea: 14% Treatment-related deaths: 3 in the tremelimumab arm, none in the CT arm	
Anti-PD1	Topalian et al (58)	I	Various advanced cancers (296 pts affected by NSCLC; HRPC; RCC; CRC and melanoma)	0.1–10 mg/kg every 2 weeks (escalating dose)	Hypophysitis: 1 pt (<1%) TSH increase: 9 pts (3%) (0.1 mg/kg: 2 pts G1–2; 1 mg/kg: 2 pts G1–2; 3 mg/kg: 2 pts G1–2; 10 mg/kg: 3 pts G1–2 + 1 pt G3–4) Hypothyroidism: 7 pts (2%) (0.3 mg/kg: 1 pt G1–2; 1 mg/kg: 2 pts G1–2; 3 mg/kg: 1 pt G1–2; 10 mg/kg: 2 pts G1–2 + 1 pt G3–4) Hyperthyroidism: 3 pts (<1%) (0.1 mg/kg: 1 pt G1–2; 3 mg/kg: 1 pt G1–2; 10 mg/kg: 1 pt G1–2 + 1 pt G3–4)	Pneumonitis: 3 pts (1%); diarrhea: 3 pts (1%); ↑ transaminases: 4 pts (2%); skin: 2 pts (1%); infusion reactions: 1 pt (<1%)

(Continued)

Table 2. Continued

Anticancer Agent	Authors	Phase	Cancer(s) (No. of Patients)	Schedule of Treatment	Incidence of Endocrine Adverse Events (All Grade)	Incidence of Other IRAEs (G3–4)
Anti-PD1-L	Brahmer et al (59)	I	Various advanced cancers (207 pts, not including melanoma)	0.3–10 mg/kg every 2 weeks (escalating dose)	Hypophysitis: 0 Hypothyroidism: 6 pts (3%): (3 mg/kg: 1 pt G1–2; 10 mg/kg: 5 pts G1–2) G1–2 autoimmune thyroiditis: 2 pts (1%) Adrenal insufficiency: 3 pts (1.5%): (3 mg/kg: 1 pt G1–2 + 1 pt G3–4; 10 mg/kg: 1 pts G1–2)	G3–4 toxicity <5% (skin, hepatitis, infusion reactions)

Abbreviations: CRC, colorectal cancer; CT, cytotoxic chemotherapy; DLT, dose-limiting toxicity; EAP, expanded access program; ED-SCLC, extensive-disease-small-cell lung cancer; G, toxicity grade according to CTC-NCI criteria; HRP, hormone resistant prostate cancer; NSCLC, non-small cell lung cancer; Pretr, pretreated; Pt(s), patient(s).

lactin levels may be elevated or low in approximately 25% of patients (29, 30). Only 1 case has been associated with diabetes insipidus (39).

Similar to classic LAH, the treatment has been glucocorticoids. Almost all patients experienced resolution of acute symptoms a few days after withdrawal of the drug and the start of high-dose glucocorticoids, levothyroxine, and sex hormone replacement (29). However, pituitary function may be impaired for a longer period of time despite glucocorticoid therapy. The time needed for resolution of symptoms and duration of replacement therapy with physiological hydrocortisone dosages (mean, 20 wk) may be considerably longer or even lifelong, considering the limited survival of these patients (23, 38). In fact, anti-CTLA4-H is the only possibly irreversible IRAE (45). Recovery of pituitary-thyroid function has been reported in 37–50% of patients (39, 40, 42), whereas gonadal axis recovered in 57% of men (29). Conversely, very few patients were able to discontinue glucocorticoid replacement, due to persistent secondary adrenal insufficiency (9, 39).

The protective role of glucocorticoids in reducing the incidence/severity of anti-CTLA4-H remains to be explored. Re-treatment with ipilimumab after interruption due to G1–2 hypophysitis seems to be safely possible (46). Importantly, high-dose glucocorticoid treatment (and replacement therapy) do not appear to decrease the antitumor effects of CTLA4 blockade (46, 47).

Thyroid side effects by anti-CTLA4-mAbs

Thyroid is the second most frequent endocrine organ involved in anti-CTLA4-mAb toxicity. However, the available clinical details are very limited. Damage to the thyroid induced by these agents presents as thyroiditis associated with antithyroglobulin and anti-thyro peroxi-

dase antibody positivity and hypothyroidism, or transient hyperthyroidism. Rare cases of Graves' ophthalmopathy have also been reported, with elevation of TSH-receptor antibodies but normal thyroid function (48, 49).

The incidence of thyreopathy induced by anti-CTLA4-mAbs (anti-CTLA4-T) varies between 0 and 4% (Table 2). In 2 studies, tremelimumab was associated with 4% thyreopathy (19, 50). With ipilimumab, the incidence seems lower (0–2%) (Table 2), with subclinical or mild (G1–2) hypothyroidism being the most frequent event. In the large phase III trial (8) leading to approval of ipilimumab, the drug was associated with thyroid disorders or abnormal thyroid function tests in approximately 2% of patients. Similar incidence of G1–2 thyroiditis is reported in trials evaluating ipilimumab as a single agent or in combination with chemotherapy in aCM (35) or other malignancies (Table 2). In a small report on 27 patients with refractory melanoma receiving a high dose of ipilimumab (10 mg/kg for 4 doses, followed by further doses in case of clinical benefit), G2 hypothyroidism occurred in 7% of cases (51).

Two cases of thyroiditis induced by ipilimumab in combination with bevacizumab have been reported (48). In a recent phase I study on pretreated or naive aCM patients (ipilimumab, 10 mg/kg every 3 wk for 4 doses, then every 3 mo; bevacizumab, 7.5 or 15 mg/kg every 3 wk), 19% (4 of 21) developed thyroiditis (33). Conversely, no cases of endocrine adverse events (AEs) were reported in 36 patients who received ipilimumab (0.1–3 mg/kg) combined with IL-2 (720 000 IU/kg every 8 h), a drug known to be associated with autoimmune thyroiditis (30). In patients with mCRPC who received ipilimumab (1–10 mg/kg escalating dose) in combination with an anti-PSA vaccine, G2 hypothy-

roidism was diagnosed in 4 (13.3%) cases at higher dose levels (5 or 10 mg/kg) (31).

The onset of anti-CTLA4-T seems to be faster compared with nonendocrine IRAEs, occurring after 2 to 4 infusions, but similar to the time of onset of anti-CTLA4-H. Most cases have a subclinical course or may be transient, consistent with a silent autoimmune thyroiditis. Alternatively, it may evolve into permanent hypothyroidism, requiring thyroid hormone supplementation (9). The administration of anti-CTLA4-mAbs did not seem to worsen previous thyroid disease.

Other endocrinopathies induced by anti-CTLA4-mAbs

PAI has been rarely reported (0.3–1.5%) with anti-CTLA4-mAbs alone or in combination with chemotherapy (8, 19, 52, 53). Yang et al (11), in a phase II study of ipilimumab in RCC, reported a case of PAI in a patient with metastasis in his residual adrenal gland who received 12 doses at 3 mg/kg. Conversely, in a phase I trial of mCRPC with combination of ipilimumab (1–10 mg/kg escalating dose) and anti-PSA vaccine, PAI was diagnosed in 3 (10%) at higher dosage (5 mg/kg, 1 patient G2; 10 mg/kg, 1 patient G2 and 1 patient G3) (31). No clinical details regarding these patients are available.

Endocrine Toxicities Induced by Anti-PD-1 and Anti-PD-1L mAbs

PD-1 is another inhibitory receptor expressed on activated T cells. PD-1L, one of its ligands, is broadly expressed on antigen-presenting cells, nonimmune tissues, and tumor cells, and its expression correlates with an unfavorable prognosis in multiple types of cancer (54). Sustained expression of PD-1 on tumor reactive T cells is associated with a functionally exhausted phenotype (55–57). Pharmacological interference with PD-1 or its ligand PD-1L increases antitumor immunity, enhances immunity in vitro, and mediates antitumor activity in preclinical models. Phase I trials with anti-PD-1 and anti-PD-1L mAbs have yielded encouraging results with durable objective responses and an acceptable safety profile.

BMS-936558, an antibody that specifically blocks PD-1 (0.1 to 10.0 mg/kg every 2 wk), was evaluated in 296 patients affected by various cancers, including aCM, non-small-cell lung cancer, mCRPC, RCC, or colorectal cancer. Cumulative response rates ranged between 18 and 28%. G3–4 drug-related AEs occurred in 14% of patients, with 3 deaths from pulmonary toxicity. Hypophysitis was observed in 1 case (<1%). No patient experienced PAI. Thyroid disease or abnormalities in thyroid function tests

were rare or sporadic. TSH increased in 9 patients (3%). Clinical hypothyroidism was diagnosed in 7 patients (2%) and hyperthyroidism in 3 patients (<1%) (58).

In another phase I trial of 207 patients with various advanced cancers (melanoma not included), BMS-936559, an anti-PD-1L (0.3–10 mg/kg at escalating doses), induced durable tumor regression (objective response rate, 6–17%) and prolonged stabilization of disease (12–41% at 24 wk). G3–4 drug-related AEs occurred in 9% of patients (59). No patient developed hypophysitis. Six (3%) patients showed hypothyroidism, and 2 (1%) had G1–2 autoimmune thyroiditis. Adrenal insufficiency was diagnosed in 3 patients (1.5%). All these side effects were reported in patients who received higher doses (3–10 mg/kg) (Table 2).

Practical Clinical Approaches

Patients on anti-CTLA4-mAbs with symptoms suggesting hypophysitis should promptly undergo pituitary MRI and pituitary function assessment. If anti-CTLA4-H is confirmed, the drug should be held, and methylprednisolone (1–2 mg/kg iv) should be given for a few days. This should be followed by oral prednisone (1–2 mg/kg), with gradual tapering over 4 weeks (25). An alternative high-dose steroid regimen is 4 mg dexamethasone every 6 hours for 7 days, followed by a gradual tapering to 0.5 mg/d and then a change to hydrocortisone at replacement dose (13, 60). Once hypophysitis resolves with appropriate treatment and adequate hormone replacement has been tailored, rechallenge with the anticancer treatment should be considered. Clearly, this decision should be made on an individual case basis. If the agent is restarted, close monitoring of pituitary function should be done (13, 60). The diagnosis and treatment of hypothyroidism is more straightforward. The ipilimumab package insert recommends testing of thyroid function and serum chemistries at baseline and before each dose. However, some experts have recommended a full endocrine panel (13, 25).

Discussion

In adults, with the exception of the direct toxicity of radiotherapy, the endocrine system is infrequently damaged by conventional anticancer treatments (61). However, cytokines, such as interferons and IL-2, and even targeted agents such as tyrosine kinase inhibitors, may cause endocrine dysfunction at a variable extent (60, 62).

Endocrine side effects induced by new immunoregulatory anticancer drugs, taken as a whole, are infrequent or rare. Particularly, the endocrine consequences of anti-PD-

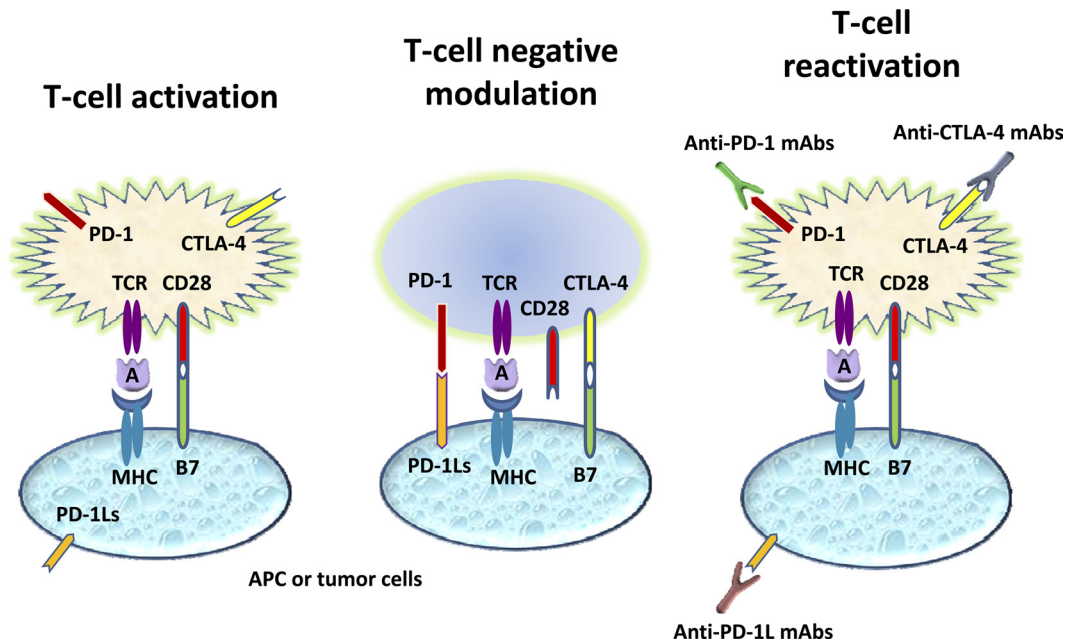


Figure 1. Suggested mechanisms for overcoming tumor-induced immune tolerance and the onset of IRAEs triggered by immune checkpoint inhibitors. Tumor antigens (A) are presented to T cells by antigen-presenting cells (APCs) via the interaction of the MHC (histocompatibility leukocyte antigen) and T-cell receptors (TCRs) representing the primary signal for activating T cells. Another costimulatory signal involving interaction between B7.1 and B7.2 on APCs and CD28 on T cells is needed to complete T-cell activation and expansion. Several coreceptors act as negative modulators of immune response at different molecular checkpoints. The CTLA4 is induced in T cells at the time of their initial response to antigen. Naive and memory T cells do not express CTLA4 on their surface, being sequestered in intracellular vesicles. After the antigen-induced TCR activation, CTLA4 is transported to the cell surface proportionally to the antigen stimulation. CTLA4 binds to B7.1 and B7.2 with greater affinity than does CD28, resulting in specific T-cell inactivation. The PD-1/PD-1L pathway is not involved in initial T-cell activation. It regulates inflammatory responses in tissues and tumor microenvironment sustained by effector T cells. Activated T cells up-regulate PD-1, and inflammatory signals in the tissues/tumor microenvironment induce the expression of PD-1Ls, which down-regulate the activity of T cells, limiting tissue damage related to immune activation. mAbs that block either CTLA4 or PD-1/PD-1L, acting as immune checkpoint inhibitors, increase cytotoxic T-cell activity by expanding T-cell activation and proliferation. The IRAEs associated with these drugs are suggested to result from this sustained/augmented activity.

1/anti-PD-1-L mAbs seem to be negligible compared with anti-CTLA4-mAbs. This might be due to the distinct roles played by immune checkpoint receptors in regulating T-cell immunity (Figure 1). CTLA4 modulates the early phases of activation of naive or memory T cells in immune response triggered by major histocompatibility complex (MHC)-peptide complexes displayed by antigen-presenting cells (63). In contrast, the PD-1/PD-1-L pathway serves to limit the activity of T cells at the time of an immune-inflammatory response, thereby protecting normal tissues from collateral destruction (63).

Interestingly, hypophysitis, a very rare disease, has emerged as a distinctive endocrine side effect of anti-CTLA4-mAbs and, most likely, as a new form of autoimmune pituitary disease. It has been occasionally reported in patients treated with anti-PD-1 mAbs (58). However, many aspects of anti-CTLA4-H remain to be clarified. Although the pathogenesis of this side effect is attributable to autoimmunity, the exact immunological mechanisms responsible for both anti-CTLA4-induced tumor regression and IRAEs remain to be fully elucidated. It was initially suggested that anti-CTLA4-mAbs may act by depleting T-regulatory cells (T-regs) (64). In another study,

the antitumor and autoimmune effects resulted from direct activation of $CD4^+CD8^+$ effector cells (30). Although $CD8^+$ cytotoxic T-lymphocytes are likely to play a major role, the specific tumor and tissue antigen(s) involved in the tumor response and toxicity are unknown. It is still unclear whether the effects result from T cells specifically acting against antigens shared by tumor and normal cells or from the concomitant activation of multiple T-cell populations with separate antihost and antitumor activities (10, 28, 64, 65). Melan-A, an antigen shared by melanoma cells and normal melanocytes, has been associated with both tumor regression and immune-related skin reactions (65). In a patient affected by aCM and treated with ipilimumab, marked melan-A-specific T-cell reactivity in tumor and skin tissue was found, with $CD8^+$ T cells localized to nevi and a simultaneous increase in melan-A-specific $CD8^+$ T cells in peripheral blood (65). It has been hypothesized that anti-CTLA4-H may be induced by antibodies directed against the pituitary gland (29), but the presence of pituitary antibodies remains to be demonstrated, and the antigen(s) involved in the autoimmune process generating anti-CTLA4-related E-IRAEs is (are) unknown.

The pathogenic mechanism of classic LAH has been better studied (14, 66), with pathological findings supporting the autoimmune pathogenesis (67). Furthermore, LAH has been recently induced in experimental mouse models by exploiting pituitary antigens (68). To our knowledge, anti-CTLA4-H has never been histologically confirmed. This is not crucial in clinical practice (69), and the invasiveness of the procedure necessary to obtain pathology specimens makes it questionable in patients with poor prognosis due to metastatic cancer. Nonetheless, pathology would be essential to obtain information on the presence of immune cells sustaining the pathogenesis of the disease. It has been recently suggested that 2 distinct entities of classic LAH can be distinguished on the basis of the prevalence of T-regs or T17-helper lymphocytes, which are CD4+ T-helper effector cells involved in multiple human autoimmune diseases (70). One of these entities, in agreement with the classical description of LAH, demonstrates an autoimmune process with T17-helper lymphocyte dominance and lack of T-regs. The other form appears as a process in which T-regs control the immune response, which may not be “self-targeted” but rather “foreign targeted” (infective agents?). Only autoimmune-sustained hypophysitis may benefit from immunosuppressive corticosteroid treatment (70) and presumably may be prevented by administration of corticosteroid.

Despite these uncertainties, most clinical and radiological features of anti-CTLA4-H appear consistent with LAH, including “*ex juvantibus*” criteria of efficacy of glucocorticoid. Anti-CTLA4-H seems to differ from classic LAH in a few aspects. Patients who develop this E-IRAE are almost all males, whereas classic LAH is strikingly more frequent among females, presumably due to the prevalence of postpartum LAH (14). However, the paucity of available reports does not allow us to emphasize that anti-CTLA4-H is prevalent in males, in opposition to most autoimmune disease. Very few patients have been described with visual field defect, owing to the relatively modest enlargement of the pituitary in anti-CTLA4-H (29, 40). At onset, neither anti-CTLA4-H, nor classic LAH offers factors predicting patients who will develop transient or persistent hypopituitarism. High-dose glucocorticoids are the standard treatment both in anti-CTLA4-H and classic LAH. However, in anti-CTLA4-H, it is not well known whether lower dosages would still be effective. Similarly, the protective role of corticosteroids in reducing the incidence/severity of anti-CTLA4-H remains to be specifically tested.

The pituitary may be the site of metastasis in patients with different cancer types (71–75). Hence, in a patient receiving an immune checkpoint inhibitor who presents with hypopituitarism and MRI evidence of pituitary en-

largement, metastatic disease must be considered in the differential diagnosis. Given the rare occurrence of diabetes insipidus in anti-CTLA4-H and its common occurrence in pituitary metastasis, this can be a differentiating criterion. Nevertheless, pituitary metastasis may occur in the absence of diabetes insipidus (76). A continuing growth of the mass despite glucocorticoid therapy should alert the physician to the possibility of a pituitary metastasis, and consideration to pituitary biopsy should be given.

The endocrine system is a frequent target of autoimmune responses and the thyroid gland is the most common organ affected by autoimmune disease (77). Consistently, older and less specific anticancer immunoregulatory agents such as interferons and IL-2 present a well-known toxicity profile, thyroid disease being the prevalent autoimmune toxicity. The incidence of thyroid abnormalities induced by these agents ranges from 5 to 50%. In addition to hypothyroidism, thyrotoxicosis and silent thyroiditis (functionally biphasic) have also been described (78–81). These agents may also worsen pre-existing autoimmune thyroid disorders. It has been suggested that interferons and IL-2 trigger thyroid disease by stimulating autoreactive lymphocytes, leading to autoimmune thyroiditis. Higher rates of thyroid autoantibody positivity (82, 83) and increased lymphocyte infiltration of the thyroid gland (84) have been found in patients treated with IL-2. Patients who underwent fine-needle aspiration had features consistent with autoimmune thyroiditis (81). Adrenal dysfunction and pituitary disease have been occasionally reported with interferon- α for hepatitis C, but not for cancer (85–89). Conversely, the endocrine autoimmunity induced by anti-CTLA4-mAbs targets mostly the pituitary rather than the thyroid. The high prevalence of pituitary autoimmunity raises some hypotheses. First, the administration of anti-CTLA4-mAbs may be responsible for an autoimmune process in which a pituitary antigen (ACTH?) triggers the inflammatory damage to pituitary. This hypothesis is supported by predominant damage to ACTH-producing cells (40). This is quite different from the clinical course of hypopituitarism secondary to other causes (adenomas, craniopharyngiomas, apoplexy, etc.), where adrenal insufficiency is a late consequence of pituitary damage. On the other hand, anti-CTLA4-T might be purely an “off-site” side effect related to the diffuse immune (auto) reactivity induced by the drugs. In this case, a genetic predisposition and/or environmental factors might have a role. However, histocompatibility leukocyte antigen status does not predict activity and toxicity of ipilimumab in melanoma patients (90). Similarly, the role of *CTLA4* gene polymorphisms and of other genes, which are involved in the development of autoimmunity (91),

needs to be better clarified in larger studies on patients treated with anti-CTLA4-mAbs.

Finally, it is well known that cytokines play a key role in the pathogenesis of several autoimmune endocrine diseases (92). In clinical studies on patients with skin and gut toxicity induced by anti-CTLA4-mAbs, the infiltration by CD4 and CD8 T cells and highly activated effector cells correlated with IRAE intensity (93). Increased serum inflammatory cytokines, as well as rapid resolution of some IRAE symptoms with the TNF- α antibody infliximab, suggested that cytokine release by activated T cells may contribute to toxicities (94). However, a “cytokine profile” has never been correlated with activity and toxicity in patients with anti-CTLA4-induced E-IRAEs.

Anti-CTLA4-H offers the opportunity to conduct prospective studies in a well-defined cohort of patients. These patients can be thoroughly characterized from an immunological point of view because they are exposed to the known causative agent. This research model may also test the reliability and predictive value of the available (and newer) diagnostic antipituitary antibodies. These antibodies, if confirmed in their diagnostic potential, might be used as predictive factors of pituitary toxicity induced by anti-CTLA4-mAbs.

Conclusion

The endocrine consequences of immune checkpoint inhibitors remain to be fully elucidated. The increasing use of ipilimumab as treatment of aCM is likely to change the epidemiology of a very rare disease such as hypophysitis. Accordingly, both oncologists and endocrinologists are obliged to be familiar with E-IRAEs induced by these new drugs, particularly with anti-CTLA4-H. This must be promptly recognized and treated. Endocrine toxicities will be more relevant if anti-CTLA4-mAbs are shown to be efficacious in the prevention of relapsing melanoma (adjuvant treatment). The mechanisms sustaining E-IRAEs triggered by new immunoregulatory anticancer agents are still poorly elucidated and require efforts aimed at the accurate characterization of the related organ diseases. In parallel, well-designed correlative studies oriented to find and validate predictive factors of autoimmune toxicity are urgently needed.

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