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REVIEW

How we treat endocrine complications of immune checkpoint inhibitors

S. A. Paschou[1], K. Stefanaki[1], T. Psaltopoulou[2], M. Liontos[2], K. Koutsoukos[2], F. Zagouri[2], I. Lambrinoudaki[3] & M.-A. Dimopoulos[2*]

[1]Division of Endocrinology, Diabetes and Metabolism, Department of Clinical Therapeutics, Alexandra Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens; [2]Division of Hematology and Oncology, Department of Clinical Therapeutics, Alexandra Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens; [3]Second Department of Obstetrics and Gynecology, Aretaieio Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

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Immune checkpoint inhibitors (ICIs) are antibodies that target certain immune checkpoints (ICs), such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death 1 (PD-1) or its ligand (PD-L1), and have emerged as a powerful new tool for oncologists. As these immune checkpoints are crucial for immunological self-tolerance, such therapies can trigger autoimmune adverse effects. Endocrine complications are among the most common, including hypophysitis, thyroid dysfunction, diabetes mellitus and primary adrenal insufficiency, while autoimmune polyendocrine syndrome type 2 (APS-2) may also present. The aim of this article is to critically appraise the literature and present (i) the biological role and function of the main ICs, (ii) the use of ICIs in the treatment of various cancer types, (iii) the endocrine complications of cancer immunotherapy with ICIs and (iv) practical recommendations for screening and management of patients with such endocrinopathies in everyday clinical practice.
Key words: immune checkpoint inhibitors, endocrine, thyroid, hypophysitis, diabetes, adrenal insufficiency

INTRODUCTION

Immune checkpoints (ICs) are small molecules that are involved in the regulation of the immune response. They play critical roles in maintaining immune homeostasis and tolerance, as they modulate the duration and amplitude of physiological immune function.[1,2] Immune checkpoint inhibitors (ICIs) are antibodies that target certain immune checkpoints, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death 1 (PD-1) or its ligand (PD-L1), resulting in T-cell activation and antitumor activity.[1,3] ICIs have emerged as a powerful new tool for oncologists and a number of such pharmacological agents are used nowadays for the treatment of various types of cancers, such as melanoma, lymphoma, lung cancer, renal cell carcinoma, urothelial carcinoma, and so on.[2,3]

However, as ICs are crucial in maintaining immunological self-tolerance and preventing autoimmune disorders, these therapies can also trigger autoimmune adverse effects. Numerous organs can be affected. Most commonly, skin, gastrointestinal system, liver, lungs and endocrine glands are involved, while less commonly other organs may be affected too.[4,5] Endocrine complications are among the most common, including hypophysitis, thyroid dysfunction, diabetes mellitus (DM) and primary adrenal insufficiency (PAI). A possible association of ICIs with hypoparathyroidism has been also reported, but it is not clear.[1,6,7] Specific endocrinopathies seem to be more common with specific agents, while combination of such therapies appears to further increase the risk of such endocrine complications. The time of onset of these endocrine adverse effects generally ranges from weeks to months after the initial dose of therapy with ICIs.[7,8] Furthermore, the frequency and severity of ICI-related endocrine adverse events range and grading systems are used in the clinical practice.[1,9]

The aim of this article is to critically appraise the literature and present (i) the biological role and function of main ICs, (ii) the use of ICIs in the treatment of various cancer types, (iii) the endocrine complications of cancer immunotherapy with ICIs, namely hypophysitis, thyroid dysfunction, DM and PAI and (iv) practical recommendations for screening and management of patients with such endocrinopathies in everyday clinical practice.

METHODS

Authors collected, analyzed and qualitatively resynthesized information on endocrinopathies after cancer immunotherapy with ICIs. English language literature was searched

*Correspondence to: Prof. and Rector Meletios-Athanasios Dimopoulos, Department of Clinical Therapeutics, Alexandra Hospital, School of Medicine, National and Kapodistrian University of Athens, 80 Vasilisis Sophias, 11528 Athens, Greece

E-mail: mdimop@med.uoa.gr (M.-A. Dimopoulos).

in PubMed until October 2020 using combinations of the terms 'checkpoints', 'checkpoint inhibitors', 'cancer immunotherapy', 'CTLA-4', 'PD-1', 'PD-L1' with terms related to endocrine complications, such as 'endocrinopathies', 'endocrine toxicity', 'hypophysitis', 'thyroid', 'diabetes' and 'adrenal' in order to identify relevant publications. MeSH terms and alike works found in the references of the studies identified were also reviewed.

Biological role and function of main ICs

ICs are small molecules on the surface of immune cells that regulate immune responses in terms of both duration and amplitude.[2] Recognition of the antigen by the naive T lymphocyte is achieved through a triple complex consisting of the antigen, the MHC (major histocompatibility complex), often called HLA (human leucocyte antigen), molecule of the antigen-presenting cell (APC) and the T-lymphocyte antigen receptor (Ag + HLA + TCR).[2,10] However, this complex recognition is not itself capable of stimulating the naive T lymphocyte for proliferation and differentiation into an active T lymphocyte; other co-stimulatory molecules are necessary. Such molecules are the B7.1 (CD80) and B7.2 (CD86) glycoproteins on the APCs and the CD28 or CD137 on T lymphocytes.[10-12] In the absence of co-stimulatory molecules, the T lymphocyte is not stimulated and switches to the anergy state. Immune cells also express other checkpoints, such as CTLA-4 and PD-1, that are inhibitory and control or blunt T cells activity.[2,12] Antibodies that have been approved for the treatment of a number of malignancies target mainly CTLA-4, PD-1, and the ligand for the PD-1 (PD-L1).[2,3]

CTLA-4

CTLA-4 is a glycoprotein that resembles the sequence of CD28, but it presents a 20-fold greater affinity for B7 glycoproteins.[13] CTLA-4, when linked to one of the B7 (CD80/CD86) molecules of the APC, transmits negative messages to T lymphocytes, limiting the production of interleukin (IL)-2 and the proliferation of stimulated cells. Therefore excessive stimulation and proliferation of T lymphocytes are avoided.[12,13] CTLA-4 is continuously expressed on the surface of T-regulatory cells (Tregs) and in that way it inhibits conventional T-cell activity. Tregs, formerly known as suppressive lymphocytes, play an important role in the immune response network, especially for peripheral tolerance.[10,12,14] CTLA-4 expression on conventional T cells can be also induced. In addition to increased affinity with CD80/CD86 and ligand-dependent signal inhibition, CTLA-4 can inhibit T-cell activation by induction of indoleamine 2,3-dioxygenase (IDO) and inhibitory cytokines production and secretion.[1,12-14] Therefore the co-stimulatory pathways are both directly and indirectly interrupted by CTLA-4.

PD-1

PD-1 is a glycoprotein that also resembles CD28, but instead of linking with the B7 (CD80/CD86) molecules, such as CTLA-4, it has specific ligands, namely PD-L1 and PD-L2.[15,16] PD-1 can be found on the surface of a number of immune cells, including macrophages, dendritic cells, B cell and T cells.[17] Normally the expression of this molecule is low, but it is increased after T-cell activation or more constantly in the case of patients with chronic infections. PD-L2 is primarily expressed on macrophages and dendritic cells, but PD-L1 expression is universal. Indeed, PD-L1 has been found on both immune and nonimmune cells, such as hepatocytes, pancreatic islet cells, endothelial cells, thyroid cells and muscle cells.[16,17] Interestingly, various tumor cells can express PD-L1 and this is one of the mechanisms that make such cells capable of escaping the host immune system.[18] Connection of PD-1 with one of its ligands induces intracellular biochemical changes that result in decrease of glucose uptake and gluconeogenesis of T cells. This phenomenon exhausts T cells, and the co-stimulatory pathways, such as CD28-CD80/86, are indirectly interrupted.[11,12,15]

In summary, even though the complete mechanisms of action are complex and remain to be further elucidated, there is a clear role of CTLA-4 and PD-1 as inhibitory ICs that regulate the immune response.

USE OF ICIs IN THE MANAGEMENT OF VARIOUS CANCER TYPES

ICIs are antibodies that target certain ICs and have emerged as a powerful new tool for oncologists.[1-3] In 2011, the Food and Drug Administration (FDA) in the United States approved ipilimumab, an anti-CTLA-4 antibody, for the treatment of malignant melanoma. Since then, anti-PD-1 antibodies, such as nivolumab and pembrolizumab, and anti-PD-L1 antibodies, such as atezolizumab, avelumab and durvalumab, have been also developed and approved for various types of malignancies. Indeed, antibodies blocking CTLA-4, PD-1 or PD-L1 are used nowadays as monotherapy or in combination with chemotherapy or with other ICIs as an effective tool for the management of a broad spectrum of cancers; i.e. melanoma, renal cell cancer, urothelial cancer, head and neck squamous cell cancer, hepatocellular cancer, Hodgkin lymphoma, triple negative breast cancer, gastric cancer, non-small-cell lung cancer (NSCLC), Merkel cell carcinoma, and so on.[1-5] Interestingly, the indications for cancer immunotherapy with ICIs are continuously increasing.

ENDOCRINE COMPLICATIONS OF CANCER IMMUNOTHERAPY WITH ICIs

As ICs are crucial for the maintenance of immunological self-tolerance and the prevention of autoimmune disorders, ICIs can trigger adverse effects of autoimmune origin.[4,5] Endocrine complications are among the most common adverse events. These include hypophysitis, thyroid dysfunction, DM and PAI. A possible association of ICIs with hypoparathyroidism has been also reported, but it is not clear.[1,7]

It has been hypothesized that the development of endocrine dysfunction may be a positive predictor of response to ICI therapy.[1] In particular, several studies have

shown that median overall and progression-free survival are significantly longer in patients with development of autoimmune disorders. Endocrine complications are thought to represent bystander effects from activated T lymphocytes and it is considered that patients with early onset of those have better therapeutic responses to ICIs.[19,20] A recent multicenter cohort study provided evidence that the development of multisystem immune-related adverse events was associated with improved survival even in patients with advanced (stage III/IV) NSCLC treated with anti-PD-L1 agents.[21] However, the exact mechanism remains elusive and this hypothesis needs further investigation.[1]

Hypophysitis

Hypophysitis, which represents the inflammation of the pituitary gland, is a rare condition in general; however, it is a common endocrine complication after therapy with ICIs. A meta-analysis including 34 studies reported hypophysitis in 85 patients among 6472 that received therapy with ICIs.[8] The incidence of hypophysitis in these patients was higher with the combination of ipilimumab (anti-CTLA-4) and nivolumab (anti-PD1) therapy (6.4%). Other large retrospective studies reported even higher percentages of hypophysitis, with a percentage between 6.7% and 13%.[22-25] ICI-related hypophysitis is found in higher rates in men, which is in contrast with the fact that hypophysitis in general affects mainly women (male to female ratio for lymphocytic hypophysitis 1 : 3).[26] Indeed, a study with 128 cases of hypophysitis after anti-CTLA-4 therapy revealed a male-to-female ratio of 4 : 1.[27] Of course, ipilimumab has been broadly used for the treatment of melanoma, which affects men more, but even in two such cohorts the percentages of hypophysitis were higher for men (15% versus 4% and 16% versus 9%, for men and women, respectively).[22,23]

Hypophysitis typically occurs within 2-3 months after ICI (mainly ipilimumab) initiation,[27] but it has been reported as long as 19 months later.[24] Symptoms typically are not specific and mostly include headache and fatigue.[23,24,28] Signs due to mass effects, such as visual defects after impingement of the optic chiasm, are rare and this is explained by the mild expansion of the pituitary gland in this type of hypophysitis. Other symptoms may include dizziness, decreased appetite or libido, nausea and weight loss.[1,6] The main consequence of ICI hypophysitis is deficiency in one or more pituitary hormones. Indeed, hypophysitis following ICI therapy often affects one axis only, which is in contrast to the conventional form of hypopituitarism. The most common deficiencies are central hypothyroidism [thyroid stimulating hormone (TSH) deficiency], central adrenal insufficiency [adrenocorticotropic hormone (ACTH) deficiency] and hypogonadotropic hypogonadism [follicle-stimulating hormone (FSH) and luteinizing hormone (LH) deficiency]. Around 80% of patients with ICI hypophysitis present one or more of the above three deficiencies.[1,8]

Central hypothyroidism is characterized by low or low normal free thyroxine (FT4) concentrations along with inappropriately low or normal TSH levels.[29] This is transient, and the thyroid axis recovers spontaneously in most cases. Central adrenal insufficiency may be present with hypotension and hyponatremia, and it can sometimes be life-threatening. It is characterized by low or low-normal cortisol levels along with low or inappropriately normal ACTH concentrations in the early morning.[30] In some cases, an ACTH stimulation test is needed to confirm the diagnosis of adrenal insufficiency. Central adrenal insufficiency appears to be permanent in most cases. This might be the only deficiency after ICIs; as it can be life-threatening, physicians should be aware of this variation in contrast to the conventional presentation of hypopituitarism.[29,30] Hypogonadotropic hypogonadism manifests biochemically with low or inappropriately normal FSH and or LH, along with low morning testosterone levels in men and low estradiol levels in premenopausal women. It is sometimes difficult to differentiate from functional hypogonadism due to advanced underlying malignant disease or ongoing therapy, such as opioids. In postmenopausal women, FSH and LH are physiologically elevated and this should be always considered for this population when hypogonadotropic hypogonadism is suspected.[31] Hypogonadotropic hypogonadism is transient and this axis recovers spontaneously in most cases. Growth hormone (GH) deficiency presents in lower percentages, but this may be due to the need of stimulating tests for certain diagnosis.[32] Insulin-like growth factor (IGF)-1 levels have been found as low or normal in these patients. Abnormal prolactin levels are less common and most times have been reported as low, while hyperprolactinemia is very rare.[22,23,28] Posterior pituitary (neurohypophysis) is not commonly affected and diabetes insipidus (DI) has rarely been reported.[33-36]

On radiographic imaging, pituitary enlargement is an indicator of high sensitivity and specificity of hypophysitis after ICI therapy. The enlargement is diffuse and mild to moderate in most cases, while thickening of the pituitary stalk may be also seen. Contrast enhancement may be homogeneous or heterogeneous.[1,25] Mass effects with pressure of the optic chiasm or other neighboring tissues are very rare. Diffuse metastatic disease should be always ruled out in these patients. Radiographic enlargement may precede the clinical diagnosis by several weeks, while it typically resolves within weeks to months.[23] Interestingly, a normal pituitary gland on imaging does not rule out hypophysitis. A study of 88 cases with hypophysitis after ipilimumab revealed that 20 (23%) presented a normal pituitary gland on MRI.[27] Imaging findings may have even resolved by the time of diagnosis, which should be always based on clinical and hormonal findings.[1,4]

Thyroid dysfunction

Thyroid dysfunction is one of the most common endocrinopathies after therapy with ICIs. The clinical spectrum is broad and varies from overt hypothyroidism to overt

thyrotoxicosis; however, the common pathophysiological basis seems to be destructive thyroiditis.[37-44] Thyroid dysfunction appears more often in patients treated with anti-PD-1 agents or after combination therapy with ipilimumab and nivolumab. Cases of thyroid dysfunction are less common after monotherapy with anti-CTLA-4 or anti-PD-L1 agents.[37-44] A meta-analysis, including 38 trials and 7551 patients in total receiving various ICIs revealed an overall incidence of 6.6% for hypothyroidism (95% CI, 5.5%-7.8%) and an overall incidence of 2.9% for hyperthyroidism (95% CI, 2.4%-3.7%).[8] However, the rates were even higher after anti-PD-1 or combination therapy groups. Hypothyroidism was found in 7% of patients after anti-PD-1 therapy and in 13.2% of cases after combination with ipilimumab and nivolumab, while hyperthyroidism was found in 3.2% after the use of anti-PD-1 agents and in 8% after combination therapy with ipilimumab and nivolumab.[8] The largest study so far resulted in even higher rates of thyroid dysfunction (up to 30% in total), with the highest rates again among patients after combination therapy with ipilimumab and nivolumab.[37]

Thyroid dysfunction typically occurs within a few weeks after ICI initiation and can happen even after a single therapeutic dose.[38] Various case series have reported a median time that ranged from 18 to 123 days[37-44]; however, the onset has been reported as early as 7 days or as late as 3 years after ICI initiation.[24,38] Most times, thyroid dysfunction initially presents as painless thyroiditis, which starts with a transient thyrotoxic phase. Thyrotoxicosis is usually mild or even asymptomatic and lasts some weeks before the patient enters into a euthyroidism or hypothyroidism phase. More often the symptoms are nonspecific, such as fatigue and weight loss. Additional clinical manifestations that may present are tremor, anxiety, heat intolerance and hyperdefecation.[1,6,7] Physical examination may reveal tachycardia or warm and smooth skin. Thyroid storm due to severe thyrotoxicosis is very rare after ICI therapy.[45,46] A few trials that studied the time for evolution to euthyroidism or hypothyroidism found a median of 4-7 weeks.[38,47] In some other cases, subclinical or clinical hypothyroidism is the initial presentation and it may be transient or permanent. Again, the symptoms are usually mild and nonspecific; fatigue and weight gain are the most commonly reported ones, while patients may also present with bradycardia, cold skin, constipation and cold intolerance.[1,6,7] Myxedema coma due to untreated hypothyroidism has been reported, but it is very rare.[48]

Autoantibodies against thyroid peroxidase (anti-TPO) and thyroglobulin (anti-Tg) have been found elevated in some, but not in all patients that develop thyroid dysfunction after immunotherapy with ICIs.[37-44] A recent study indicated that high titer of anti-TPO or anti-Tg prior to therapy appears to be related to ICI thyroid dysfunction.[49] In general, the data so far show that thyroid autoantibodies are not necessary, but they represent a risk factor. Stimulating autoantibodies for the TSH receptor [TSH receptor antibodies (TRAb) or thyroid stimulating immunoglobulin (TSI)] were negative in the majority of patients studied.[37-44] In very few cases only, TRAb were positive which means that destructive thyroiditis may co-exist with Graves' disease.[50,51] Measurement of TSH, FT4 concentrations [and triiodothyronine (T3) if needed] are enough to provide a proper diagnosis in most cases. In thyrotoxicosis after thyroiditis, FT4 levels are more increased compared with T3 levels due to destruction and leakage of stored thyroxine (T4) into blood, compared with hyperthyroidism when T3 is produced in higher levels after stimulation of the thyroid gland. Of course, when hypothyroidism is present, it should be carefully differentiated between primary and central hypothyroidism, because hypophysitis should be always considered and assessed in these patients.[1,4-6]

Diabetes mellitus

DM is a rare but severe and possibly life-threatening endocrine complication after therapy with ICIs. Most cases that have been reported so far are after anti-PD-1 or anti-PD-L1 therapy.[1] Cases are too few to reach conclusions regarding demographics; the onset has occurred after a single or after 17 doses and from 1 week to 12 months.[52-59] The hyperglycemia is of rapid onset, while swift progression to endogenous insulin deficiency has been consistently found. If the situation is not suspected and not treated promptly and properly with insulin, the risk for diabetic ketoacidosis (DKA) is high.[1] Indeed, in the majority of the case described so far (70%), DKA was the reason for diagnosis.[52-59] DKA may present with nausea, vomiting, abdominal pain, tachypnea or lethargy and coma. Earlier symptoms of hyperglycemia include polyuria, polydipsia, and weight loss, while in other cases hyperglycemia may be detected incidentally after a laboratory test for plasma glucose. Glycated hemoglobin (HbA1c) is elevated in most cases of DM after ICIs. However, due to the acute onset of hyperglycemia most times, HbA1c might not be a good screening parameter. It seems that this type of DM ends up in complete endogenous insulin deficiency with low or undetectable C peptide levels. Long-term daily insulin therapy is then needed.[1,6,7]

The exact pathogenesis of destruction of beta pancreatic cells is not clear. The majority of cases had no preexisting prediabetes or diabetes. Furthermore, they did not have other autoimmune diseases.[52-59] Islet autoantibodies, such as GADA (glutamic acid decarboxylase autoantibodies), IA2 (islet autoantibodies) IAA (insulin autoantibodies) and anti-ZnT8 (zinc transporter autoantibodies) were positive in 50% of patients tested.[1] The most prevalent were GADA, in fact results were always positive in cases where autoantibodies were detected. Interestingly, a number of patients with DM after ICIs have HLA types that are known to increase genetic susceptibility for type 1 DM.[57,60,61] Pancreatic imaging with ultrasound, CT or MRI was available in some studies and has been unremarkable or has shown atrophy or enlargement or other findings indicative of diffuse inflammation.[57,61-63]

Primary adrenal insufficiency

PAI is a rather rare complication of ICIs. More specifically, this endocrine complication has been reported in higher

rates for men and after treatment with ipilimumab, nivolumab and pembrolizumab or their combinations.[64-68] Conclusions for the time of onset cannot be reached, while a parameter that possibly underestimates the incidence of PAI after treatment with ICIs is the fact that the exact cause of adrenal insufficiency (primary or secondary due to hypophysitis) is not clearly reported in clinical trials. Indeed, there are few cases in studies so far reported as definite PAI, while many more have been reported as possible PAI.[1,68] Symptoms and signs are nonspecific and include fatigue, orthostatic hypotension and abdominal discomfort; however, a possible adrenal crisis could be life-threatening. Hyponatremia and hyperkalemia are often seen, while hypoglycemia and hypercalcemia are less common.[69]

PAI is characterized by low cortisol levels along with elevated ACTH concentrations, which differentiates from secondary adrenal insufficiency due to hypophysitis. Furthermore, in that case mineralocorticoid deficiency is also present, with low aldosterone and elevated renin levels, as all zones of the adrenal cortex are affected.[69] Elevated levels of adrenal autoantibodies have been reported in a few patients only.[64] Importantly, bilateral adrenal metastases or hemorrhage leading to adrenocortical impairment should always be excluded in any patient with cancer. Abdominal imaging can be helpful; bilateral enlarged adrenal glands with smooth borders are indicative of adrenalitis due to ICIs.[1,6]

Autoimmune polyendocrine syndrome

Autoimmune polyendocrine syndrome (APS) describes the presence of two or more autoimmune endocrine conditions in patients with genetic susceptibility. There are few cases (~30 in total) reported and published in the literature with presentation of APS-2 after cancer immunotherapy with ICIs so far. In these patients, two or more autoimmune endocrinopathies (PAI, thyroid dysfunction, type 1 diabetes) presented after such a therapy. Most of them were treated with PD-1 inhibitors and had a high-risk HLA genotype (HLA-DR4 allele).[70]

PRACTICAL RECOMMENDATIONS FOR SCREENING AND MANAGEMENT

First of all, patients, family members or physicians that take care of these patients should receive early and detailed education about the clinical profile of possible endocrine complications of ICIs prior to initiation and throughout treatment, ideally by a joint team of oncologists and endocrinologists. They should be able to recognize and promptly report various symptoms or signs, such as extreme weakness, unusual headache patterns, vision changes, increased sweating, rapid heartbeat, weight loss or weight gain, mood changes, constipation or diarrhea, deepening of the voice, changes in urination, polydipsia, extreme or low hunger, nausea or vomiting and abdominal pain.[4,5,71] At baseline, morning measurements of TSH, FT4, cortisol, glucose and electrolyte levels should be performed in all patients. These laboratory tests should be repeated every 4-6 weeks as part of routine monitoring. Another measurement 4-6 weeks after the last cycle of immunotherapy maybe necessary for identification of late-onset complications. An essential part of the routine monitoring is the clinical investigation of symptoms suggestive of endocrine adverse effects.[1,4,5,6,71]

When thyroid disorder is suspected or indicated by the initial tests, measurement of thyroid autoantibodies, namely anti-TPO (against thyroid peroxidase) and anti-Tg (against thyroglobulin) for hypothyroidism and TRAb (TSI, autoantibody stimulating TSH receptor) for hyperthyroidism, is helpful.[4,71] If morning cortisol levels are low (<5 μg/dl), this is indicative of adrenal insufficiency and ACTH measurement can differentiate for primary (×2 upper limit) or secondary adrenal insufficiency. ACTH stimulation test (250 μg i.v.) is the gold standard tool to establish diagnosis in such cases or to provide diagnosis in cases of indeterminate morning cortisol results (5-18 μg/dl). Peak cortisol levels below 18 μg/dl at 30 or 60 min indicate adrenal insufficiency. In case of primary adrenal insufficiency, adrenal computed tomography (CT) is helpful.[69,71]

If low cortisol is accompanied by low ACTH, hypophysitis is suspected and then the laboratory tests should be completed with measurement of LH, FSH and testosterone in men or estradiol levels in premenopausal women. These tests should be also performed when fatigue, loss of libido and mood changes are present. Measurement of prolactin and IGF-1 levels do not really change the therapeutic strategy approach for these patients, but they can be also measured.[1,4-6] In patients with multiple endocrine abnormalities and in those with headaches or visual defects, a pituitary MRI should be also considered. DI is rare, but monitoring is valuable especially after starting glucocorticoids.[1,4] When hyperglycemia is present, laboratory evaluation should include urine testing for ketosis and blood pH measurement for prevention of DKA. Due to the acute onset of hyperglycemia in most occurrences, HbA1c might not be a good screening parameter. However, it may reveal the glycemic status of previous months, as type 2 diabetes mellitus (T2DM) is a common disease. Glutamic acid decarboxylase, IA2, IAA and ZnT8 autoantibodies are highly specific for autoimmune diabetes, while insulin and C-peptide levels can also assist for the evaluation of the endogenous insulin secretion.[4,5]

As APS-2 may present after diagnosis of an autoimmune endocrine disease induced by ICIs, close monitoring for the development of other autoimmune endocrinopathies is necessary. Some groups recommend genotyping for HLA and risk stratification according to alleles.[70] The appropriate clinical and laboratory evaluation of patients on immunotherapy with ICIs for possible endocrinopathies is presented in Table 1.

Adverse events in general but also endocrine complications, after ICIs specifically, are categorized in five grades, in order of increasing toxicity: grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening and grade 5 = death.[9] In general, grade 4 toxicities warrant

permanent discontinuation of ICIs. However, endocrinopathies that are well controlled by appropriate hormone replacement are an exception to this rule, indicating the importance of early identification and treatment of these complications. Of course, holding ICI treatment until the patient is stabilized on hormone replacement, especially in the case of adrenal insufficiency, is often necessary.[4,5] Grading of endocrinopathies after therapy with ICIs and appropriate management is presented in Table 2.

When adrenal insufficiency is diagnosed, replacement therapy with hydrocortisone (15-25 mg/day) applied in two to three daily doses is indicated. Alternatively, other types of corticosteroids in equivalent doses can be used if needed for other therapeutic reasons. When the cause is PAI, fludrocortisone for mineralocorticoid replacement once daily is also required. The starting dose is 50-100 μg and it is titrated according to electrolytes, salt craving and blood pressure.[69] In grade 2, outpatient treatment at two to three times of initial dose to manage symptoms is recommended. All patients must be properly trained for sick day rules and dose adjustments of corticosteroid replacement therapy, and they should all carry an emergency card, in order to avoid a crisis. When severe symptoms are present, parenteral administration of high-dose hydrocortisone (100 mg at presentation) is required. This should be followed by appropriate fluid resuscitation and 100-200 mg hydrocortisone/24 h via continuous i.v. therapy or 6-hourly injections. Normal saline is usually administered i.v., but sometimes hypoglycemia is also present and should be treated with i.v. administration of dextrose. When the clinical and biochemical picture has improved, treatment can be changed to oral hydrocortisone (60 mg/24 h), progressively reduced to replacement dose.[4,5,69,71,72] When hypophysitis and more than one endocrine deficiency are present, hydrocortisone should always be started several days before levothyroxine, to avoid adrenal crisis. When hypogonadotropic hypogonadism is diagnosed, testosterone in men or estrogen/progestogen therapy in women may be initiated, but only in those without relevant contraindications. GH replacement is contraindicated in patients with active malignancy.[4-6] The use of high-dose systemic corticosteroids (prednisolone 1 mg/kg/day) in patients with ICI hypophysitis has been described; however, there is no robust evidence to support this therapeutic approach and it should be reserved for the few severe cases.[22,71,72]

In case of clinical hypothyroidism (TSH >10 mIU/l or TSH 4-10 mIU/l with low FT4 and/or with symptoms), levothyroxine replacement dose of ~1.1 μg/kg/day is usually needed. This is the starting dose mostly used in cases of subclinical hypothyroidism, in general. For elderly patients or for those with cardiovascular comorbidities the best approach is titrating up from a low dose, starting at 25-50 μg per day. Exclusion of cortisol deficiency before initiation of levothyroxine treatment is very important.[4,6] In very rare cases, admission for i.v. therapy may be necessary if signs of myxedema (bradycardia, hypothermia) are present.[1,4] When hyperthyroidism is suspected, initial close follow-up and monitoring of TSH, FT4 and T3 every 2-3 weeks is necessary. This is important to differentiate between permanent hyperthyroidism and transient leakage of thyroid hormones into the blood due to destructive thyroiditis that may ultimately lead to hypothyroidism. Positive TRAb and elevated T3 levels can help in the diagnosis of hyperthyroidism. In that case, treatment with methimazole (or propylthiouracil, which is used less often nowadays) is indicated, while beta blockers are always helpful.[1,4,5] Treatment with corticosteroids has often been described; however, despite the destructive pathophysiological basis of the thyroid dysfunction, there is no evidence that their use limits thyrotoxicosis or shortens the thyrotoxicosis phase. Therefore the use of corticosteroids for thyroid dysfunction after ICIs could be additively considered only in severe cases (≥grade 3) or in the presence of thyroid orbitopathy.[1,4,71] DM after ICIs is characterized by insulin deficiency in the majority of cases, therefore treatment with both long-acting insulin at bedtime and short-acting insulin before meals is needed. Total daily requirements can be estimated at 0.3-0.4 units/kg/day for more patients, half units for long-acting and half for divided prandial

Table 1. Evaluation of patients on ICIs immunotherapy for possible endocrinopathies

Baseline	• Clinical evaluation for symptoms: Extreme weakness, unusual headache patterns, vision changes, increased sweating, rapid heartbeat, weight loss or weight gain, mood changes, constipation or diarrhea, deepening of the voice, changes in urination, polydipsia, extreme or low hunger, nausea or vomiting, abdominal pain • Laboratory evaluation: Morning TSH, FT4, cortisol, glucose, electrolytes
Every 4-6 weeks and 4-6 weeks after the last cycle	• Clinical evaluation for symptoms • Laboratory evaluation: Morning TSH, FT4, cortisol, glucose, electrolytes
Additional tests	
If hypothyroidism suspected	• Anti-TPO, anti-TG
If hyperthyroidism suspected	• T3 • TSH, FT4, T3 every 2-3 weeks to diagnose persistent hyperthyroidism or hypothyroidism (due to destructive thyroiditis) • TRAb (TSI)
If cortisol low	• ACTH • Consider ACTH stimulation test (250 μg i.v.) • Adrenal CT, if primary adrenal insufficiency
If hypophysitis suspected	• ACTH, LH, FSH, testosterone (men) or E2 (women) • PRL, IGF-1 can be also measured • Pituitary MRI, if multiple endocrine abnormalities, headaches or visual defects • DI is rare, but monitoring is important in some cases
If hyperglycemia	• pH, urine ketones • Autoantibodies (GADA, IA2, IAA, anti-ZnT8) • C peptide

ACTH, adrenocorticotropic hormone; CT, computed tomography; DI, diabetes insipidus; E2, estradiol; FSH, follicle stimulating hormone; FT4, free thyroxine; GADA, glutamic acid decarboxylase autoantibodies; IA2, islet autoantibodies; IAA, insulin autoantibodies; ICI, immune checkpoint inhibitors; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; MRI, magnetic resonance imaging; PRL, prolactin; T3, triiodothyronine; TG, thyroglobulin; TPO, thyroid peroxidase; TRAb, TSH receptor antibodies; TSH, thyroid stimulating hormone; TSI, thyroid stimulating immunoglobulin; ZnT8, zinc transporter.

Table 2. Management of endocrinopathies after ICIs according to grading

Endocrinopathies	Grade 1 Asymptomatic or mild symptoms	Grade 2 Moderate symptoms	Grade 3 Severe but not life-threatening symptoms	Grade 4 Life-threatening consequences	Grade 5 Death
Hypophysitis Inflammation of the pituitary gland	• Low cortisol (<5 μg/dl or <18 μg/dl after ACTH stimulation test), low ACTH and asymptomatic or mild symptoms • Consider holding ICIs • Hydrocortisone (15-25 mg/day) in 2-3 doses or equivalent • If central hypothyroidism also present, start levothyroxine always several days after hydrocortisone and monitor with FT4 levels • If hypogonadism also present, testosterone in men or estrogen/progestogen therapy in women, only in those without contra-indications • GH replacement is contraindicated in patients with active malignancy • Endocrine consultation	• Low cortisol and moderate symptoms • Hold ICIs until symptoms resolve • Management as in G1, but ×2-3 initial dose hydrocortisone	• Severe symptoms • Hold ICIs until symptoms resolve • Hospitalize for i.v. fluids and hydrocortisone (100 mg at presentation) • High-dose systemic corticosteroids (prednisolone 1 mg/kg/day) should be reserved for few severe cases	• Life-threatening symptoms • Management as in G3	–
Hypothyroidism Decrease in production of thyroid hormones	• TSH 4-10 mIU/l, normal FT4 and asymptomatic • Continue ICIs • TSH every 4-6 weeks	• TSH >10 mIU/l or TSH 4-10 mIU/l with low FT4 and/or with moderate symptoms • Hold ICIs until symptoms resolve • Levothyroxine (starting dose ~1.1 μg/kg/day or 25-50 μg for elderly and patients with CVD) • TSH every 6 weeks while titrating to optimal dose • FT4 can be used in the short term (2 weeks) to ensure adequacy	• Severe symptoms • Management as in G2 • Endocrine consultation	• Life-threatening symptoms • Management as in G3 • Hospitalize patient for i.v. therapy if signs of myxedema	–
Hyperthyroidism Increase in production of thyroid hormones	• TSH <0.4 mIU/l and asymptomatic or mild symptoms • Continue ICIs • TSH, FT4, T3 every 2-3 weeks to diagnose persistent hyperthyroidism or hypothyroidism (due to destructive thyroiditis)	• Low TSH and moderate symptoms • Hold ICIs until symptoms resolve • Beta blockers • TRAb (TSI) measurement • Methimazole if persistent hyperthyroidism • TSH, FT4, T3 every 4-6 weeks • Endocrine consultation	• Severe symptoms • Management as in G2 • Consider corticosteroids	• Life-threatening symptoms • Management as in G3 • Hospitalize patient with concern of thyroid storm	–
Diabetes mellitus Increase of blood glucose levels	• Fasting glucose >126 mg/dl and asymptomatic or mild symptoms • Continue ICIs • Close follow-up of blood glucose	• Fasting glucose >160 mg/dl and moderate symptoms • Hold ICIs until symptoms resolve • pH and urine ketones • Insulin if persistent hyperglycemia and insulin deficiency (0.3-0.4 units/kg/day, half units for long-acting and half for divided prandial doses) • Close follow-up of blood glucose • Endocrine consultation	• Severe symptoms • Management as in G2	• Life-threatening symptoms • Management as in G3 • Hospitalize patient for i.v. insulin therapy in case of DKA	–
Primary adrenal insufficiency Disorder of the adrenal cortex	• Low cortisol (<5 μg/dl or <18 μg/dl after ACTH stimulation test), high ACTH (×2 upper limit) and asymptomatic or mild symptoms • Consider holding ICIs • Hydrocortisone (15-25 mg/day) in 2-3 doses or equivalent • Fludrocortisone (starting dose 50-100 μg) • Endocrine consultation	• Low cortisol and moderate symptoms • Hold ICIs until symptoms resolve • Management as in G1, but ×2-3 initial dose hydrocortisone	• Severe symptoms • Hold ICIs until symptoms resolve • Hospitalize for i.v. fluids and hydrocortisone (100 mg at presentation)	• Life-threatening symptoms • Management as in G3	–

ACTH, adrenocorticotropic hormone; CVD, cardiovascular disease; DKA, diabetic ketoacidosis; FT4, free thyroxine; G, grade; GH, growth hormone; ICIs, immune checkpoint inhibitors; i.v., intravenous; T3, triiodothyronine; TRAb, TSH receptor antibodies; TSH, thyroid stimulating hormone; TSI, thyroid stimulating immunoglobulin.

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doses. Suspicion for DKA should be high and if diagnosed, hospitalization with i.v. hydration and insulin administration is necessary.[1,4,5,71,72]

CONCLUSIONS

As the immune checkpoints that ICIs inhibit are crucial for immunological self-tolerance, these therapies can trigger autoimmune adverse effects. Endocrine complications are among the most common, including hypophysitis, thyroid dysfunction, DM and PAI. Physicians dealing with such patients should be aware of the ICI-related endocrine adverse events, the clinical presentation and laboratory findings, as well as their frequency and severity. Appropriate screening and management of these patients with close collaboration of oncologists and endocrinologists is essential. As survival is increasingly improving, the monitoring and management of long-term consequences are extremely important and the need for development of joint clinics is obvious.

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DISCLOSURE

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