AUCTORES
Globalize your Research

Journal of Endocrinology and Disorders
Sami T. Azar

Open Access

Review Article

Hypophysitis due to Immune Checkpoint Inhibitors

Rawaa El Sabbagh[1], Nadim S. Azar[2, 3], Assaad A. Eid[3] and Sami T. Azar[1*]
[1]Division of Endocrinology and Metabolism, American University of Beirut
[2]Department of Internal Medicine, American University of Beirut
[3]Department of Anatomy, Cell Biology and Physiological Sciences, American University of Beirut
Corresponding Author: Sami T. Azar, MD, Professor of Medicine, 3 Dag Hammarskjold Plaza, 8th New York, NY 10017, USA.
Received date: October 27, 2020; Accepted date: December 01, 2020; Published date: February 09, 2021
Citation: Rawaa El Sabbagh, Nadim S. Azar, Assaad A. Eid and Sami T. Azar (2021) Hypophysitis due to Immune Checkpoint Inhibitors *J. Endo and Dis*; 5(1); DOI:10.31579/2640-1045/055
Copyright: © 2021, Sami T. Azar, This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Immune checkpoint inhibitors are antineoplastic drugs associated with adverse events that result from unleashing the immune system against self-antigens while attacking neoplastic cells. Endocrinopathies are among the most common associated adverse events and hypophysitis is a frequent endocrine side effect of this treatment.

We conducted a systematic search of the literature in 2 databases: PubMed and Medline. Articles that reported endocrine adverse events of immune checkpoint inhibitors were reviewed.

Hypophysitis is most commonly seen with cytotoxic T-lymphocytes associated protein 4 (CTLA-4) inhibitors and can result in different anterior pituitary hormones deficiencies. Monitoring for this complication is of particular interest due to the life-threatening nature of secondary adrenal insufficiency and thyroid dysfunction if not promptly recognized and treated.

Hypophysitis is the most common endocrinopathy seen and is usually treated by adequate hormonal replacement. The use of high dose corticosteroids has not been established as a treatment of this endocrine toxicity. Hormonal screening should be a part of baseline laboratory testing of all patients undergoing treatment with immune checkpoint inhibitors.

Keywords: immune check point inhibitors, toxicity, endocrinopathy, CTLA-4 inhibitors, anti-PD1, anti-PDL1, hypophysitis

Abbreviations:

ACTH: Adrenocorticotrophic Hormone
Anti-TPO: Thyroid Peroxidase antibodies
Anti-ZnT8: Zinc Transporter Protein 8 antibodies
CTLA-4: Cytotoxic T-lymphocytes Associated Protein 4
DKA: Diabetic Ketoacidosis
DM: Diabetes Mellitus
GH: Growth Hormone
HbA1c: Hemoglobin A1c
ICPi: Immune Checkpoint Inhibitors
IrAEs: Immune Related Adverse Events
MRI: Magnetic Resonance Imaging
PAI: Primary Adrenal Insufficiency
PD-1: Programmed Cell Death Protein
PDL-1: Programmed Death-Ligand 1
PDL-2: Programmed Death-Ligand 2
TRAb: TSH Receptor Antibodies
TSH: Thyroid Stimulating Hormone
TFT: Thyroid Function Tests

Introduction

Immune checkpoint inhibitors are new antineoplastic medications with expanding use in different types of cancer. The specific mechanism of action of these drugs results in a new type of adverse events related to the immune system [1]. Pituitary dysfunctions are among the most common adverse events observed. The increase in the use of immune checkpoint inhibitors and the improved survival of patients treated by these medications make the identification of endocrine side effects essential [1]. In fact, these endocrinopathies can affect the quality of life of the patients, and might be life-threatening in some cases if not promptly recognized and treated [1].

Over the past several years, the use of immune checkpoint inhibitors (ICPi) has changed the management and prognosis of many advanced solid tumors [1]. These drugs are monoclonal antibodies that block immune checkpoints that are present on the surface of T-cells to ensure immune self-tolerance, resulting in an increase of the T-cells ability to attack the cancer cells [2]. (Figure A and B).

Figure A: CTLA-4 pathway

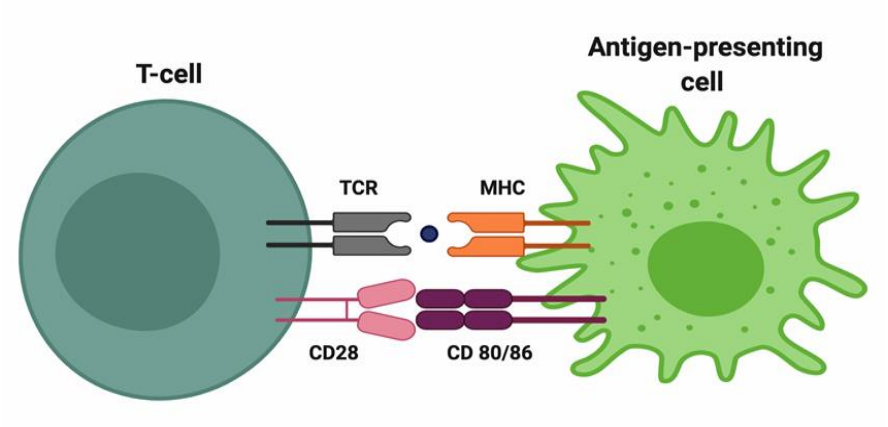

Figure A-1: T cell activation in response to the tumor associated antigen requires 2 signals. The first signal is achieved when the major histocompatibility complex (MHC) on the surface of the antigen-presenting cell (APC) recognizes the T-cell receptor (TCR) of the T cell. The second signal is the binding of CD80/86 (also known as B7) on the APC cell with the CD28 receptor on the T cell. This will lead to the activation of the immune response against the tumor cells.

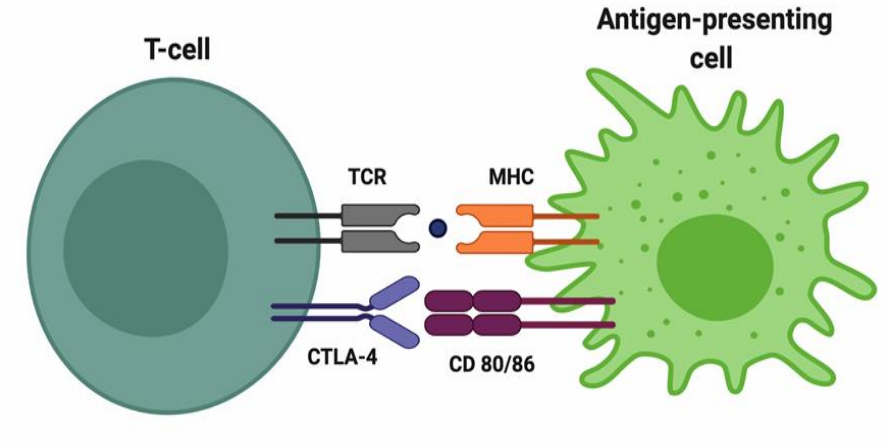

Figure A- 2: CTLA-4 (cytotoxic T-lymphocyte-associated antigen-4), a homolog of CD28, is a checkpoint present on T cells that limits proliferative response of activated T-cell by competing with CD28 for its ligand CD80/86. This inhibition will interrupt the second signal.

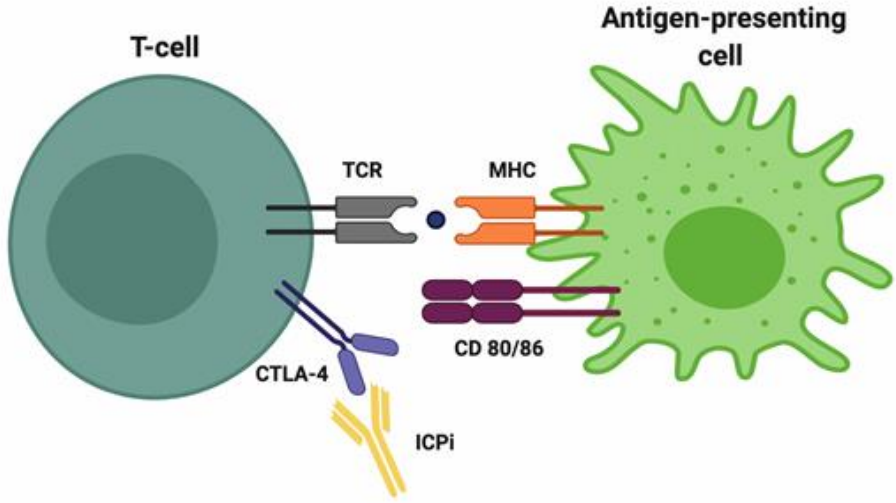

Figure A-3: Monoclonal antibodies against CTLA-4 block CTLA-4 and will lead to T- cell activation and proliferation against the tumor cells.

Figure B: PD-1- PD-L1 pathway

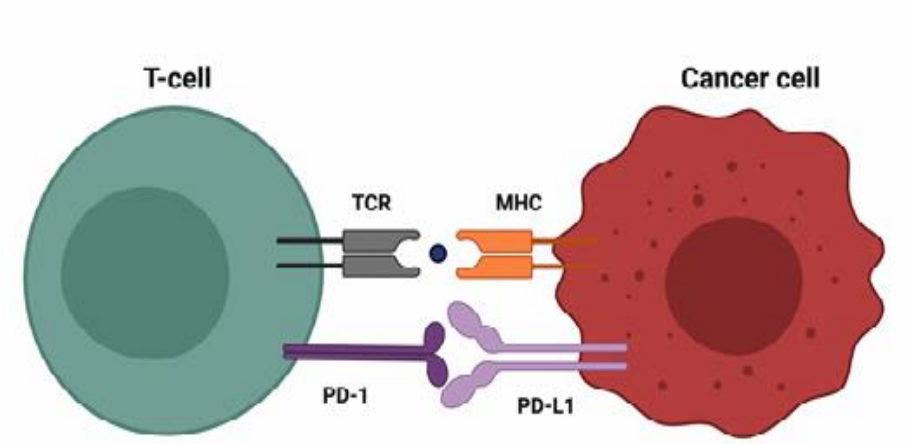

Figure B-1: PD-1 is a checkpoint present on the surface of T cells. When PD-1 binds to its ligands PD-L1/2 present on APC and cancer cells, this will result in the inhibition of T cell activity in favour of tumor survival.

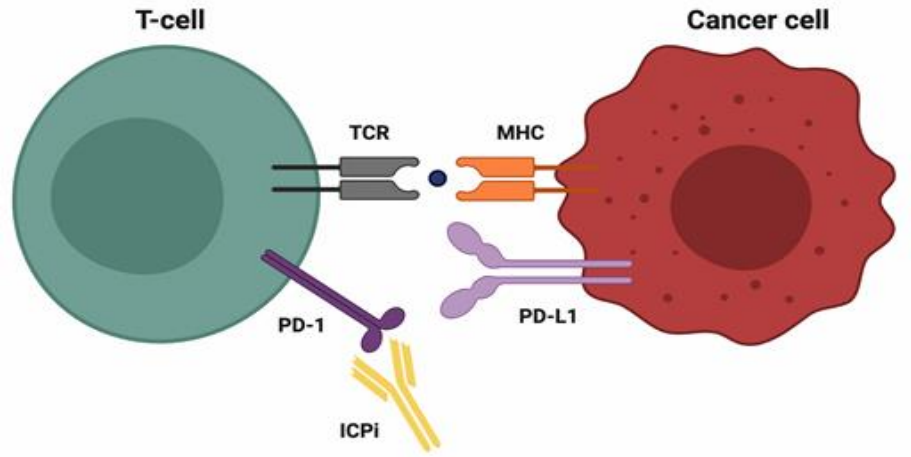

Figure B-2: Monoclonal antibodies against PD-1 or PDL-1/2 will lead to the activation of the immune response against the tumor cells.

Currently, seven immune checkpoint inhibitors are approved for the treatment of different advanced solid tumors: a cytotoxic T-lymphocytes associated protein 4 (CTLA-4) inhibitor Ipilimumab; three programmed cell death protein (PD-1) inhibitors: Nivolumab, Pembrolizumab and Cemiplimab; and three programmed death-ligand 1 (PD-L1) inhibitors: Atezolizumab, Avelumab and Durvalumab [3-9]. Table 1 summarizes the different ICPi available and their various clinical indications.

Drug (Trade name)	ICPi Class	Indications
Ipilimumab (Yervoy)	CTLA-4 inhibitor	Melanoma
Nivolumab (Opdivo)	PD-1 inhibitor	Melanoma Non-small cell lung cancer Renal cell carcinoma Hodgkin lymphoma Head and neck squamous cell carcinoma Urothelial Carcinoma Colorectal Cancer Hepatocellular carcinoma Small cell lung cancer
Pembrolizumab (Keytruda)	PD-1 inhibitors	Melanoma Non-small cell lung cancer Head and neck squamous cell carcinoma Hodgkin Lymphoma Urothelial Cancer Gastric or GEJ Cancer

		Cervical Cancer Hepatocellular carcinoma Merkel Cell Carcinoma Renal cell carcinoma Small cell lung cancer Esophageal carcinoma Endometrial cancer
Cemiplimab (Libtayo)	PD-1 inhibitors	Cutaneous Squamous Cell Carcinoma
Atezolizumab (Tecentriq)	PD-L1 inhibitors	Urothelial Carcinoma Non-squamous NSCLC Small cell lung cancer Breast cancer
Avelumab (Bavencio)	PD-L1 inhibitors	Merkel Cell Carcinoma Urothelial Cancer Renal cell carcinoma
Durvalumab (Imfinzi)	PD-L1 inhibitors	Bladder Cancer NSCLC Small cell lung cancer
Combination (Ipilimumab+ Nivolimab)	CTLA-4 inhibitor + PD-1 inhibitor	Melanoma RCC Colorectal Cancer

Abbreviations: GEJ: Gastro esophageal junction cancer, **HCC:** Hepatocellular carcinoma, **HNSCC:** Head and neck squamous cell carcinoma, **NSCLC:** Non-small cell lung cancer, **RCC:** Renal cell carcinoma, **SCLC:** Small cell lung cancer

Table 1: Summary of Immune Checkpoint Inhibitors and their clinical indications

ICPi are associated with immune related adverse events (IrAEs) that result from unleashing the immune system against self-antigens while attacking neoplastic cells [10]. Endocrinopathies are among the most common associated IrAEs, affecting the pituitary gland, the thyroid gland and to a lesser extent the pancreas, the adrenal gland and the parathyroid glands [11].

Search

We conducted a systematic search of the literature in 2 databases: PubMed and Medline. Articles that reported endocrine adverse events of immune checkpoint inhibitors were reviewed. We used the following keywords or corresponding Medical Subject Heading terms: "ipilimumab," "nivolumab," "pembrolizumab," "atezolizumab," "Cemiplimab" "Avelumab" "Durvalumab" "CTLA-4 inhibitors" "PD-1 inhibitors" "PDL-1 inhibitors" "immune checkpoint inhibitors" "endocrinopathies" "hypophysitis" "endocrine side effects". We also reviewed references of published trials and review articles.

Discussion

Pituitary dysfunction observed with ICPi is due to hypophysitis, which is the inflammation of the pituitary gland resulting in hormonal deficiency (12). Based on the results of a recent meta-analysis [13] the incidence of hypophysitis differs among ICPi regimens. It is higher with combination therapy (ipilimumab with nivolumab) reaching 8%. A lesser incidence is observed with CTLA-4 inhibitors monotherapy, estimated to be around 3.8%. Finally, the incidence of hypophysitis is very rare with PD-1 inhibitors (1.1%) [14]. The median time to onset of hypophysitis also varies depending on the molecule. It may occur early on in the setting of combination therapy (an average mean of 1 month), while with anti-CTLA-4 and anti-PD-1 therapy it may occur at 2-3 months and 3-5 months respectively [14, 15].

The pathogenesis of hypophysitis with ICPi is not clear. In a murine model of hypophysitis induced by ipilimumab, CTLA-4 was found to be expressed in pituitary cells, which could explain the higher incidence of hypophysitis with ipilimumab [16]. Some studies have shown that when ipilimumab binds to CTLA-4 on the pituitary cells, type II and type IV hypersensitivity reactions are induced, leading to hypophysitis [17, 18]. In one study, it was shown that antibodies against the anterior pituitary cells, namely the thyrotropic, corticotropic and gonadotropic cells, developed de novo in the serum of mice receiving the anti-CTLA-4 antibody [17]. This finding suggests that the humoral immune response may play a role in hypophysitis secondary to CTLA-4 inhibitors [17].

The symptoms of hypophysitis are not specific and depend on the affected pituitary axis, with headache being the most common symptom at presentation [17]. Secondary adrenal insufficiency is present in the majority of patients (91%) and can be differentiated from primary adrenal insufficiency (PAI) by the lack of hyperkaliemia or hypotension, while hyponatremia can be found in both conditions. Secondary hypothyroidism and hypogonadism are also common with an incidence reaching around 80% for each disorder. Patients with hypophysitis secondary to CTLA-4 inhibitors rarely present with diabetes insipidus, which can result in a loss of the posterior bright spots on T1-weighted MRI [19]. Growth hormone (GH) and prolactin deficiency are also very rare IrAEs [16]. Prolactin levels can be checked in those with secondary hypogonadism as hyperprolactinemia can result in hypogonadotropic hypogonadism. Prolactin may be either elevated or decreased in patients undergoing anti-CTLA4 therapy [20].

The diagnosis of hypophysitis due to immune checkpoint inhibitors is based on clinical, biochemical and/or radiological findings [21]. The workup should include free T4, TSH, cortisol level and an ACTH level ideally taken before starting steroids replacement. The measurement of gonadotropins is helpful in the diagnosis of pituitary insufficiency. However, the levels of gonadotropins and testosterone may be decreased in the setting of stress or with the administration of certain medications [22]. Because the treatment with GH analogs is contraindicated in the setting of active malignancy, GH screening is not recommended [23]. Magnetic resonance imaging (MRI) of the pituitary is the preferred imaging modality to make the diagnosis of hypophysitis and differentiate it from metastasis, infundibulo-hypophyistis, apoplexy and adenoma. In a recent review of case reports [19], in the majority of cases (108/222), imaging by MRI showed a mild to moderate enlargement of the pituitary gland. Normal MRI was found in 49 cases, pituitary atrophy was found in

3 cases and sella abnormality was seen in 3 cases. MRI was not reported/done in 22 cases. MRI may show thickening of the pituitary stalk [24] and sometimes heterogeneous gland enhancement on injection. Impingement of the optic chiasm is rarely seen, which explains the low incidence of visual disturbance in hypophysitis secondary to ICPi [16, 17, 18, 21, 23, and 24].

The management of hypophysitis requires hormonal replacement [25, 26]. In patients presenting with cardiovascular instability, adrenal crisis should be suspected and treated. Dexamethasone 4-10 mg should be used in cases where immediate blood withdrawal is not feasible before initiating steroids because dexamethasone does not ross react with cortisol in the radioimmunoassay. Once the patient is stable, the diagnosis can be confirmed by testing [27].

In central adrenal insufficiency, hydrocortisone replacement consists of daily doses of 15 to 20 mg, titrated to the patients' clinical needs [28, 29]. Patients should be educated about sick day rules to increase their steroids dose and seek medical advice emergently [29]. In central hypothyroidism, thyroid hormone replacement can be initiated at low doses 0.8 mcg/kg/day and titrated gradually, according to free T4, due to the possible recovery of the thyroid axis [30, 31]. Glucocorticoid replacement should always precede thyroid replacement by days to avoid adrenal crisis precipitation [32].

The role of high dose glucocorticoids in the treatment of acute hypophysitis is highly debatable in the literature [33, 34, and 35]. Although it is recommended in the ipilimumab insert package [36]. In a retrospective study of 98 patients with hypophysitis due to ipilimumab, higher dose of glucocorticoids was associated with worse outcomes (shorter overall survival and time to treatment failure) compared with patients on replacement dose of steroids. This could be explained by the fact that high dose steroids might inhibit the effect of T lymphocytes and counteract the effect of immunotherapy [33].

The development of hypophysitis in the setting of ICPi use does not contraindicate the continuation of therapy. However, the decision to withhold it in the acute phase of hypophysitis depends on the severity of the symptoms [25].

The data available on the recovery of the pituitary gland after ICPi-induced hypophysitis is limited by the small sample size in most studies. Secondary adrenal insufficiency seems to be permanent in the majority of cases while secondary hypothyroidism and secondary hypogonadism have higher chances of recovery [33]. Patients with hypophysitis should be monitored closely, both clinically and biochemically, to adjust their hormonal replacement doses [25]. MRI of the pituitary gland after 3 months from the date of diagnosis is recommended by some guidelines in order to monitor pituitary inflammation and rule out the presence of metastasis [21].

Systematic hormonal screening before immunotherapy is not routinely recommended by all oncologic societies [25, 26]; however; it is recommended to keep a low threshold for pituitary hormonal testing in patients taking ipilimumab who present with non-specific symptoms. We recommend screening all patients undergoing ICPi therapy with TSH, FT4, 8 am serum cortisol, LH, FSH, testosterone/estradiol before the first immunotherapy course and at each immunotherapy infusion during the first 6 months. In asymptomatic patients with a normal hormonal workup, the frequency of hormonal monitoring can be decreased to every 2 months in the second 6 months of therapy and only in cases of suggestive symptoms thereafter [25, 26].

Guidelines	Hormonal Screening	Monitoring after hypophysitis
American Society of Clinical Oncology (ASCO) 2018 [25]	No screening recommended ahead of treatment	Monitor Free T4 for titration of thyroid hormone replacement
European Society for Medical Oncology (ESMO) 2017 [26]	Screening before the first immunotherapy course: **For anti-CTLA-4 and combination immunotherapy** TFT, adrenal function tests and gonadotropin hormonal tests During immunotherapy: **Anti-CTLA-4 and combination therapy:** TFT, adrenal function tests and gonadotropin hormonal tests *First 12 weeks:* every 3 weeks prior to every infusion *For 3 months after last infusion:* at every follow-up visit (every 6 weeks) *After 3 months of the last infusion*: every 3 months **Anti-PD-1/PDL-1:** TFTs at follow-up: Refer to thyroid disorders in Table 3 *No indication for adrenal function tests or gonadotropin tests*	N/A

French Society of Endocrinology (SFE) 2018 [29]	Screening before the first immunotherapy course: 8-am cortisol TSH and Free T4 In males: LH, FSH and total testosterone In non-menopausal females*: LH, FSH and estradiol in menopausal females: FSH *Pituitary MRI ahead of immunotherapy is not recommended.* During immunotherapy: *First 6 months:* At each immunotherapy course: 8-am cortisol** TSH, free T4 In males: total testosterone In non-menopausal females: interview on menstrual disorder *Second 6 months**** Same hormonal monitoring as above every 2 months *After 12 months:* No monitoring indicated unless suggestive symptoms are present *Systematic pituitary MRI during follow-up is not recommended.*	During immunotherapy: *First 6 months:* At each immunotherapy course: Clinical and hormonal assessment (same as screening) At 3 months after diagnosis: MRI pituitary to rule out pituitary metastasis *Second 6 months:* Every 3 months: Clinical and hormonal assessment (same as screening) *After 12 months:* Twice yearly: Clinical and hormonal assessment (same as screening)
Society for Immunotherapy of Cancer (SITC) 2017 [26, 34]	Screening before the first immunotherapy course: early morning ACTH and cortisol TSH and free T4 During immunotherapy: Before each cycle of immunotherapy: TSH and free T4 *Routine monitoring with early morning ACTH and cortisol levels should be considered (every month for 6 months, then every 3 months for 6 months then every 6 months for 1 year).*	In central adrenal insufficiency: **First year**: every 3 months am cortisol ACTH +/- low dose cosyntropin stimulation test **After the first year**: Same hormonal monitoring as above every 6 months In central hypothyroidism: TFTs after 6–8 weeks of initiation of hormonal replacement **First year:** TFTs every 3 months **After first year**: TFTs every 6 months.

Abbreviations: FSH: Follicule stimulating hormone, LH: Luteinizing hormone, N/A: Not available, TFTs: Thyroid function tests
* in case of menstrual disorder
** in the absence of glucocorticoid drug treatment
*** If the patient is asymptomatic and hormonal work-up is normal
**** combination of anti-CTLA4 + anti-PD-1/PD-L1

Table 2: Hypophysitis induced by ICPi therapy- Screening and monitoring recommendations in Guidelines

Conclusion

ICPi therapy appears to play an important role in the development of hypophysitis. The pathogenesis of this mechanism, although incompletely elucidated, has been hypothesized to have different immunological mechanisms. Symptoms of hypophysitis induced by ICPi therapy are non-specific and mainly diagnosed on the basis of clinical, biochemical and radiologic findings. As for the management of hypophysitis, it consists mainly of hormone replacement. Different ICPi therapies work on different receptors and as such have a varied scale of ensuing physiological effects. Finally, different screening protocols and guidelines during and after immunotherapy are detailed.

The use of ICPi in different types of cancer is expected to increase in the upcoming years. This relatively new modality of treatment is challenging for all specialists, including endocrinologists, due to the unknown pattern of adverse effects. It is thus necessary to devise new studies regarding the therapy, in regards to pathophysiology, adverse reactions and treatment efficacy.

Conflict of Interest

The authors of this review have no conflict of interest to disclose

References

1. Kreamer KM. (2014) Immune checkpoint blockade: a new paradigm in treating advanced cancer. *J Adv Pract Oncol.* 5: 418-31.
2. Pardoll DM. (2012) The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 12:252-64.
3. Hodi FS. (2010) Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. *N Engl J Med*. 363:711-23.
4. Weber JS. (2015) Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol.* 16(4):375-84.
5. Robert C. (2015) Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med*. 372:2521-32.
6. Migden MR. (2018) PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma. *N Engl J Med*. 379:341-51.
7. Rittmeyer A. (2017) Atezolizumab versus docetaxel in patients with previously treat ed non-small-cell lung cancer (OAK): a phase 3, open-label, multicenter randomised controlled trial. *Lancet.* 21389(10066):255-65
8. Patel MR. (2018) Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. *Lancet Oncol*. 19(1):51-64.
9. Antonia SJ. (2017) Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. *N Engl J Med*. 377:1919-29
10. Postow MA. (2018) Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. *N Engl J Med*. 378:158-68
11. Barroso-Sousa R. (2018) Endocrine Dysfunction Induced by Immune Checkpoint Inhibitors: Practical Recommendations for Diagnosis and Clinical Management. *Cancer*. 124:1111-21.
12. Solinas C. (2018) Cancer immunotherapy-associated hypophysitis; *Semin Oncol*. 45(3):181-86.
13. Barroso-Sousa R. (2018) Incidence of Endocrine Dysfunction Following the Use of Different Immune Checkpoint Inhibitor Regimens: A Systematic Review and Meta-analysis. *JAMA Oncol*. 4(2):173-82.
14. Scott ES. (2018) The spectrum, incidence, kinetics and management of endocrinopathies with immune checkpoint inhibitors for metastatic melanoma. *Eur J Endocrinol*. 178:175–82.
15. Torino F. (2013) Endocrine side-effects of anti-cancer drugs: mAbs and pituitary dys- function: clinical evidence and pathogenic hypotheses. *Eur J Endocrinol*. 169: R153–64.
16. Caturegli P. (2016) Hypophysitis Secondary to Cytotoxic T-Lymphocyte-Associated Protein 4 Blockade: Insights into Pathogenesis from an Autopsy Series. *Am J Pathol.* 186(12):3225-35.
17. Iwama S. (2014) Pituitary expression of ctla-4 mediates hypophysitis secondary to administration of ctla-4 blocking antibody. *Sci Transl Med*. 6:230ra45.
18. Laurent S. (2013) The engagement of CTLA-4 on primary melanoma cell lines induces antibody-dependent cellular cytotoxicity and TNF-alpha production. *J Transl Med.* 11:108.
19. Tan MH. (2019) Spectrum of immune checkpoint inhibitors-induced endocrinopathies in cancer patients: a scoping review of case reports. *Clin Diabetes Endocrinol*. 5:1. doi: 10.1186/s40842-018-0073-4.
20. Girotra M. (2018) The Current Understanding of the Endocrine Effects From Immune Checkpoint Inhibitors and Recommendations for Management *JNCI Cancer Spectr*. 2(3): pky021.
21. Briet C et al. (2018) Expert opinion on pituitary complications in immunotherapy. *Ann Endocrinol* (Paris). 79(5):562-8.
22. Smith CG. (1982) Drug effects on male sexual function. *Clin Obstet Gynecol*. 25(3):525-31.
23. Molitch ME. (2011) Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 96(6):1587-609.
24. Faje AT. (2014) Ipilimumab-induced hypophysitis: a detailed longitudinal analysis in a large cohort of patients with metastatic melanoma. *J Clin Endocrinol Metab.* 99(11):4078-85.
25. Brahmer JR. (2018) Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 36(17):1714-68.
26. Haanen J. (2017) Management of Toxicities from Immunotherapy: ESMO Clinical Practice Guidelines. *Ann Oncol* 28 (suppl 4): iv119–iv42.
27. Puar TH. (2016) Adrenal Crisis: Still a Deadly Event in the 21st Century. *Am J Med*. 129(3):339.
28. Fleseriu M. (2016) Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 101(11):3888-921.
29. Reznik Y. (2018) SFE/SFEDP adrenal insufficiency French consensus: introduction and handbook. *Ann Endocrinol* (Paris) 79:1–22.
30. Scott ES. (2018) The spectrum, incidence, kinetics and management of endocrinopathies with immune checkpoint inhibitors for metastatic melanoma. *Eur J Endocrinol.* 178:175–82.
31. Albarel F, Gaudy C, Castinetti F, Carré T, Morange I, Conte-Devolx B, et al. (2015) Long-term follow-up of ipilimumab-induced hypophysitis, a common adverse event of the anti-CTLA-4 antibody in melanoma. *Eur J Endocrinol*. 172:195–204.
32. Banitt PF. (1986) Addisonian crisis after thyroid replacement. *Hosp Pract* (Off Ed). 21(5):132–4.
33. Min L. (2015) Systemic high-dose corticosteroid treatment does not improve the outcome of ipilimumab-related hypophysitis: a retrospective cohort study. *Clin Cancer Res*. 21:749–55.
34. Byun DJ. (2017) Cancer immunotherapy- immune checkpoint blockade and associated endocrinopathies. *Nat Rev Endocrinol.* 13:195–207.
35. Corsello SM. (2013) Ipilimumab-induced endocrinopathies: when to start corticosteroids (or not). *Cancer Chemother Pharmacol*. 72(2):489–90.
36. Bristol-Myers Squibb. (2018) Full prescribing information for Yervoy (ipilimumab).