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Endocrinological toxicities related to immunotherapy combinations for advanced renal cell carcinoma: Practical expert-based management recommendations

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ABSTRACT

Nowadays immune-based combinations are the standard first-line treatment for metastatic renal cell carcinoma and involve the use of either two immunotherapy agents or an immunotherapeutic drug associated with a tyrosine kinase inhibitor. Treatment-related toxicity is the primary cause of drug discontinuation or dose reduction. A thorough understanding of the prevention and management of adverse events of the immune-based combinations is critical to ensure the success of treatment. Endocrinological toxicities during treatment with immune-based combinations are frequent and often manageable. However, in some cases, diagnosis can be complex, and the treatment requires multidisciplinary discussion. In addition, it is often challenging to determine which agent in the combination is responsible for a specific toxicity. In this review, we analyze the evidence regarding treatment-related endocrinopathies in renal cell carcinoma first-line therapy. We also discuss monitoring strategies to diagnose endocrinological adverse events and provide some practical tools for their daily management.

1. Introduction

Kidney cancer accounts for 2.2 % of all cancer diagnoses worldwide, with more than 431,000 new cases each year and approximately 180,000 deaths(Sung et al. 2021). Although 75 % of patients affected by renal cell carcinoma (RCC) are diagnosed at early stages, 30 % of them will develop metachronous distant metastases (Siegel et al. 2021). Patients with metastatic disease have always been deemed incurable, with a 4-year overall survival (OS) rate of less than 50 % (Albiges et al. 2020). In recent years, several new systemic treatments have been introduced, especially combination regimens containing immune checkpoint inhibitors (ICIs). The first milestones of modern RCC treatment were developed to tackle angiogenesis, a critical hallmark of RCC pathogenesis and development (Delcuratolo et al. 2023). However, identification of the unique tumor microenvironment that characterizes RCC has opened the door to more advanced therapeutic strategies. These approaches consider the synergistic effect of ICIs and anti-angiogenic drugs (especially tyrosine kinase inhibitors, TKIs). Several phase 3 trials have demonstrated the superiority of the combination of anti- programmed death protein-1 (PD-1) or its ligand-1 (PD-L1) ICIs and multitarget TKIs over single-agent TKIs (Plimack et al. 2023; Motzer et al. 2022). Moreover, the combination of the anti-PD-1 monoclonal antibody nivolumab with the anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) ipilimumab has shown superiority over TKI in treatment--naïve patients with metastatic RCC (Albiges et al. 2020). However, despite the significant reduction in the risk of death (between 32 % and

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40 %) achieved by these combinations, an increased risk of adverse events (AEs) has been reported in all trials (Rizzo et al. 2022). Indeed, while the administration of ICIs is characterized per se by the risk of developing immune-related adverse events (IRAEs), RCC represents a unique entity, as some organs frequently involved in IRAEs, especially those of the endocrine system, are also potential targets of TKIs-related toxicities. In this review, we aim to summarize evidence regarding treatment-related endocrinopathies in patients affected by RCC treated with TKIs and ICIs as first-line therapy. Thyroid toxicities induced by immunotherapy combinations in RCC pivotal trials are described in Table 1. Furthermore, we discuss how to monitor patients during treatment to properly diagnose endocrinopathies and provide some practical tools for daily management.

2. Methods

This was a narrative review conducted searching literature evidence in PubMed database. We designed a search strategy that includes the key terms endocrinological adverse events and renal cell carcinoma in conjunction with the following classes of therapies: immune checkpoint inhibitors, and antiangiogenic therapies. We primarily focused on literature that included systematic reviews, meta-analyses, and analyses of clinical trials. We examined the credibility and validity of the chosen literature and identified any contradictory findings. We selected the works that could be useful to provide practical expert-based management recommendations according to the objective of the review. After selecting publications, pertinent data was retrieved, and endocrinological adverse events were classified according to the organs involved.

3. Results and discussion

3.1. Endocrine adverse events during tyrosine kinase inhibitor treatment

Endocrine toxicities induced by TKIs may affect virtually all endocrine axes. Among these, thyroid disorders are the most prevalent, followed by adrenal, pituitary, and gonadal dysfunction. Typically, these toxicities manifest as hormone deficiencies, which are effectively managed through replacement therapy. Managing endocrine toxicities seldom necessitates interrupting or reducing TKI doses. However, prompt diagnosis and management are imperative to alleviate symptoms, mitigate the risk of life-threatening situations (De Leo et al. 2023).

Table 1
Rate of thyroid adverse events in phase III trials for advanced renal cell carcinoma.

Trial	Phase	Median follow-up	Thyroid AEs Combo vs Sunitinib
CHECKMATE 214 Nivolumab + Ipilimumab vs Sunitinib (1:1) n = 1096 (Albiges et al., 2020; Motzer et al., 2018)	3	55 months	**Hypothyroidism**: 17 % vs 27 % **Hyperthyroidism**: 12 % vs 2 %
KEYNOTE 426 Pembrolizumab + Axitinib vs Sunitinib (1:1) n = 861 (Rini et al., 2019), *2021, Plimack 2023*	3	43 months	**Hypothyroidism**: 38 % vs. 35 % **Hyperthyroidism**: 12 % vs. 3,5 %
CHECKMATE 9ER Cabozantinib + Nivolumab vs Sunitinib (1:1) n = 651 (Choueiri et al., 2021; Motzer et al., 2022; Powles et al., 2024)	3	44 months	**Hypothyroidism**: 36.9 % vs 30.6 % **Hyperthyroidism**: 10 % vs. 1 %
CLEAR Lenvatinib + Pembrolizumab vs Lenvatinib + Everolimus (1:1:1) n = 1069 (Motzer et al., 2021), *2023*	3	33 months	**Hypothyroidism**: 56.8 % vs. 26.8 %

Endocrine adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Typically, these events range from grade 2 to grade 3, with grade 4 or 5 occurrences being rare (Castinetti et al. 2018; Fallahi et al. 2021).

3.1.1. Thyroid dysfunction

Hypothyroidism is a well-known adverse event of TKIs, while hyperthyroidism is less common and typically manifests as destructive thyroiditis, often transient and manageable with symptomatic therapy. The incidence of hypothyroidism during TKI treatment ranges from 40 % to 45 %, albeit with variability among studies attributed to factors such as the specific drug, dosage, duration of treatment, and patient characteristics (De Leo et al. 2023). For instance, in phase III trials with axitinib for advanced renal cell carcinoma, hypothyroidism occurred in 20 % of patients (Motzer et al. 2013; Quinn et al. 2021); whereas dedicated studies revealed rates as high as 68 % during axitinib treatment (Takada et al. 2019). Similarly, in a phase III trial comparing cabozantinib versus everolimus in advanced RCC, hypothyroidism was reported in 20 % of patients receiving cabozantinib (Choueiri et al. 2015) with comparable findings in studies involving lenvatinib for unresectable hepatocellular carcinoma (Tada et al. 2020). Moreover, combined treatment with immune checkpoint inhibitors (ICIs) and TKIs has been associated with an even higher incidence of thyroid dysfunction, particularly hypothyroidism, affecting over 60 % of patients (Tsai et al. 2024; Lee et al. 2022). Factors predisposing patients to hypothyroidism include being female, older age, and pre-existing thyroid disease (Tsai et al. 2024; Lechner et al. 2018; Illouz et al. 2009; Lee, Lee et al. 2023). The mechanisms responsible for hypothyroidism during TKI treatment remain incompletely understood. However, studies suggest that destructive thyroiditis may contribute significantly. Observational studies have also noted a decrease in thyroid volume and the emergence of thyroperoxidase antibodies, indicating that thyroid autoimmunity may contribute to hypothyroidism development (Pani et al. 2015). Additional mechanisms include thyroperoxidase inactivation and reduced iodine uptake by thyrocytes (Mannavola et al. 2007), allegedly consequent to hypoxic damage of TKI on thyrocytes. During axitinib treatment, an inappropriate elevation of serum TSH levels has been reported, possibly due to a decreased biological activity of TSH (Ohba et al. 2013). TKIs may also affect TSH metabolism and clearance (Verloop et al., 2013). Moreover, an increased dose of levothyroxine (FT4) was required to maintain normal TSH levels in thyroidectomized patients during TKI treatment (Brassard et al. 2011), suggesting an alteration in thyroid hormone metabolism. TKIs, with their antiangiogenic effects, increase the activity of hypoxia-induced factor 1 and induce the activity of type 3 deiodinase, enhancing the peripheral metabolism of thyroid hormone (Abdulrahman et al. 2010; Kappers et al. 2011). Finally, patients on levothyroxine replacement therapy may require increased doses due to malabsorption resulting from gastrointestinal toxicity (nausea, vomit, diarrhea) caused by TKIs. Thyroid dysfunction is an early adverse event in patients treated with TKIs or TKIs combined with ICI. Hypothyroidism occurs sooner in patients receiving combination therapy with ICI and TKI (around 8 weeks after treatment initiation) (Tsai et al. 2024), compared to patients taking TKIs alone (28–36 weeks) (Lechner et al. 2018).

3.1.2. Adrenal dysfunction

Adrenal insufficiency has been documented in patients undergoing TKI treatment. Subclinical adrenal insufficiency has been reported in 55–60 % of patients undergoing lenvatinib therapy for differentiated thyroid carcinoma (Colombo et al. 2019; Valerio et al. 2023; Monti et al. 2021).

It is hypothesized that TKI-induced alteration of physiological angiogenesis may contribute to adrenal damage (Patyna et al. 2008). The early diagnosis of adrenal insufficiency is challenging, but crucial, as it can be fatal if not rapidly diagnosed and treated (Barnabei et al. 2022). Symptoms of adrenal insufficiency, including fatigue, typically

improve with the initiation of cortisone acetate replacement therapy, reducing the need for TKI interruption or dose reduction (Colombo et al. 2022).

3.1.3. Gonadal dysfunction

Hypogonadism is common among oncological patients, and treatment with TKIs can further disrupt the hypothalamic-pituitary-gonadal axis. Prospective studies conducted on male patients with metastatic RCC have revealed notable effects of TKIs on hormone levels. A prospective study in metastatic RCC observed the occurrence of hypogonadism in patients treated with sunitinib and pazopanib, although not with axitinib. There was a correlation between testosterone levels and the duration of TKI treatment, suggesting that hypogonadism may represent a chronic side effect of TKI therapy (Afshar et al. 2019). TKIs have also been reported to adversely affect oocyte and sperm maturation, affecting overall fertility potential (Rambhatla et al. 2021).

3.1.4. Pituitary dysfunction

Unlike ICI, TKIs are not typically associated with hypophysitis. However, they can disrupt several pituitary axes, including the pituitary-thyroid, pituitary-adrenal, and pituitary-gonadal axes (as discussed in the other sections).

3.1.5. Parathyroid and bone metabolism dysfunction

TKIs have been implicated in dysregulation of bone metabolism affecting both osteoblast development and activity, leading to decreased bone formation, and osteoclast activity. Consequently, parathyroid hormone levels increase to compensate for the decreased efflux of calcium and phosphate from bone to the extracellular space (Berman et al. 2006). Observational studies have indicated that up to 24 % of patients treated with lenvatinib developed hypocalcemia during treatment. Both PTH-dependent and PTH-independent mechanisms have been implicated in this adverse event (De Leo et al. 2023).

3.1.6. Metabolic disease

TKIs can interfere with glucose metabolism. However, different TKIs may have contrasting effects, with some drugs associated with hyperglycemia and others with hypoglycemia. In around 10–20 % of cases, axitinib, sorafenib, pazopanib, sunitinib, have been linked to hypoglycemia (Mugiya et al. 2024). The diagnosis of diabetes during TKI treatment follows the usual criteria: fasting glucose $>$ 126 mg/dL (7.0 mmol/L) on two assays or any glucose level $>$ 200 mg/dL (11.1 mmol/L) associated with signs of hyperglycemia. Glucose levels $<$ 70 mg/dL (3.9 mmol/L) are considered hypoglycemia (Buffier et al. 2018). Hyperglycemia can manifest with signs and symptoms such as polyuria, dehydration, polydipsia, weight loss, blurred vision, anorexia, nausea, fatigue, and diarrhea (Fallahi et al. 2021). Special attention should be paid to cases of hypoglycemia, particularly if symptomatic. Adjustments or interruptions in diabetes treatment may be necessary.

3.2. Endocrine adverse events during Immune checkpoints inhibitor treatment

Endocrine adverse events related to ICIs treatment are relatively frequent. The most common are:

3.2.1. Thyroid alterations

Thyroid dysfunction is the most common endocrine adverse event reported, with a prevalence of 2–40 % for hypothyroidism and 2–30 % for hyperthyroidism (Byun et al. 2017; Chang et al. 2019; Barroso-Sousa et al. 2018; Iglesias, 2018) (Fig. 1).

In most cases, patients exhibit transient thyrotoxicosis followed by hypothyroidism. However, the specific pathogenesis underlying ICIs-induced hypothyroidism remains unclear, making it challenging to predict which patient could be at risk. Some studies have evaluated the relevance of the TSH levels before starting ICIs showing that basal TSH levels in patients who developed hypothyroidism during ICIs treatment were significantly higher than in patients without hypothyroidism (Iyer et al. 2018; Olsson-Brown et al. 2020; Brilli et al. 2021). Brilli et al. identified that a baseline TSH value lower than 1.72 mIU/l can identify patients who will not develop thyroid dysfunction during ICIs treatment ($P = 0.0029$). Furthermore, multivariate analysis demonstrated that both TSH levels and the presence of anti-thyroid antibodies (ATAbs), before ICI treatment, are independently associated with the development of thyroid dysfunction. (Brilli et al. 2021)

Another Italian study including patients treated mainly with nivolumab and pembrolizumab showed that basal TSH levels above 1.67 mIU/L associated with ATAbs are risk factors for the development of

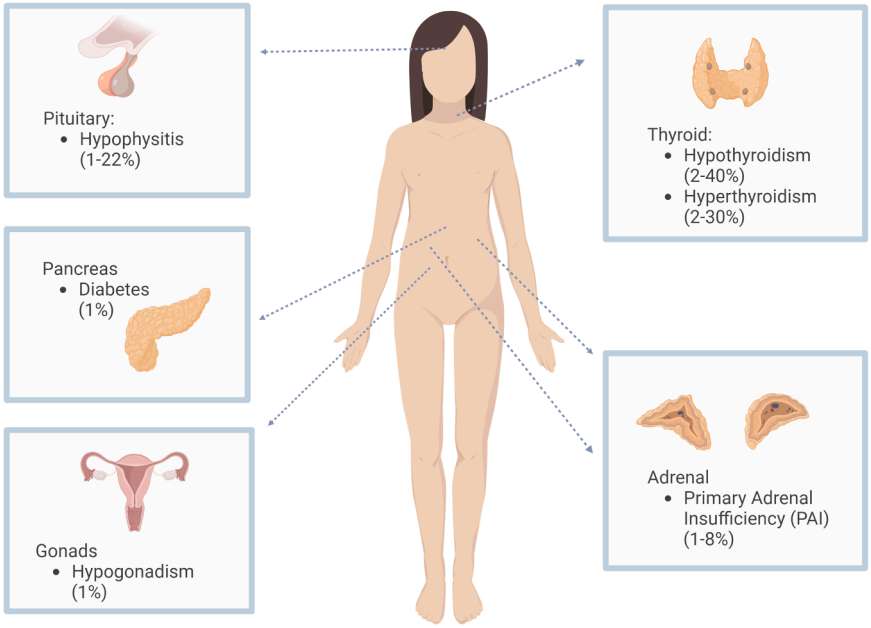

Fig. 1. Illustration of the main endocrine immune-related adverse events (IRAEs) during immune checkpoint inhibitors (ICIs) treatment and their prevalence. Created with Biorender.com.

thyroid dysfunction during ICIs treatment. Moreover, the authors demonstrated that patients who developed a thyroid alteration had a longer survival rate compared to those with normal thyroid function (Luongo et al. 2021). A familial history of thyroid diseases has been reported as a potential risk factor for early identification of patients at greater risk of developing thyroid dysfunction during ICI treatment (Ruggeri et al. 2023).

While the association between ICIs treatment and hypothyroidism is well established, only a few cases of autoimmune hyperthyroidism (Graves' disease) have been reported, mainly during therapy with nivolumab (Iadarola et al. 2019).

3.2.2. Pituitary alterations

Hypophysitis, including central hypocortisolism or multiple pituitary hormone deficiencies, is a relevant IRAE in patients undergoing anti-CTLA-4 and combination treatment and appears to be dose-dependent (Albarel et al., 2023). According to available data, the prevalence ranges between 0.5 % and 22 % of patients (Fig. 1). ICI-induced hypophysitis occurs more frequently in men over 60 years of age, typically manifesting 2–4 months after starting anti-CTLA-4 and 3–6 months after starting PD-1 or PD-L1 Ab therapy. An earlier onset is often observed during combination treatment (Jessel et al. 2022; Dalmazi et al. 2019).

Hypophysitis developed during PD-1 blockade is mostly characterized by isolated and severe ACTH deficiency, without mass effect and imaging abnormalities. Conversely, hypophysitis during anti-CTLA-4 treatment presents mild pituitary enlargement, headache, and panhypopituitarism. Although the mechanisms of ICI-induced hypophysitis remain unclear, the appearance of autoantibodies against TSH, FSH, and ACTH-secreting pituitary cells, as well as CTLA-4 expression in prolactin (PRL) and TSH-secreting cells have been hypothesized. Likely related to the pituitary expression of CTLA-4, the incidence of hypophysitis seems higher with anti-CTLA-4 compared to anti-PD-1 therapy (Barroso-Sousa et al. 2018; Iwama et al. 2014). Similar to thyroiditis, the development of hypophysitis could be considered a positive predictor of response to immunotherapy (Faje et al. 2018; Johnson et al. 2023; Kotwal et al. 2022).

3.2.3. Adrenal alterations

Primary Adrenal insufficiency (PAI) is a rare IRAE, which occurs especially in patients treated with nivolumab or ipilimumab in monotherapy or combination treatment (Albarel et al., 2023) (Fig. 1).

As a premise, we should consider that at least some of the so-called PAIs described in the literature could actually be the result of an undetected hypophysitis (leading to a picture of secondary hypoadrenalism) or could be iatrogenic, induced by the discontinuation, not always progressive, of corticosteroid therapies (Byun et al. 2017; Barroso-Sousa et al. 2018; Atkinson and Lansdown, 2022).

Indeed, fewer than 20 cases have been clinically and biochemically confirmed as anti-CTLA-4 or anti-PD-1/PD-L1-induced PAIs (Atkinson and Lansdown, 2022; Hodi et al. 2010; Hescot et al. 2018; Ryder et al. 2014; Haissaguerre et al. 2018). The mechanism of immunotherapy-induced PAI is unknown but appears related to the immune destruction of the adrenal glands (Min and Ibrahim, 2013).

PAI appears to occur more frequently with PD-1 antibodies (0–4.3 % with pembrolizumab and 0–3.3 % with nivolumab) than with CTLA-4 inhibitors (0.3–1.5 % with ipilimumab). In the few cases reported in the literature, the majority of patients were male, with a mean age of 52 years and a median onset of PAI 10 weeks after starting ICI treatment (Shi et al. 2021; Postow et al. 2018; Joshi et al. 2016; Spagnolo et al. 2022).

There are no specific clinical signs for ICI-induced PAI and 3 different scenarios have been reported: a typical acute presentation with nausea, vomiting, diarrhoea, hypoglycaemia, hypotension requiring prompt treatment, a more progressive and non-specific subacute picture, and an isolated hyponatremia (Paepegaey et al., 2017a; Trainer et al. 2016; Atkinson and Lansdown, 2022).

3.2.4. Hypogonadism

There is limited data regarding the impact of ICIs on gonadal function. A recent WHO analysis and a French Pharmacovigilance database reported a significant increase in the risk of hypogonadism for ICIs, particularly secondary hypogonadism in the context of panhypopituitarism (Bai et al., 2020; Garon-Czmil et al. 2019). Hypophysitis with associated hypogonadism has been recorded in patients treated with ipilimumab with a variable prevalence (Faje et al. 2014; Albarel et al., 2015). Interestingly, gonadotropin deficiency persisted in 16 % of cases at almost 3 years of follow-up. Nevertheless, the current incidence of ICI-related hypogonadism remains unknown since hormone assessments was not performed systematically (Ryder et al. 2014).

In addition to central hypogonadism, ICIs treatment can induce direct injury to testicular tissue leading to primary hypogonadism and infertility. Two patients with metastatic melanoma treated with ipilimumab-nivolumab and pembrolizumab have been reported to developed bilateral orchitis and epididymo-orchitis (Brunet-Possenti et al. 2017; Quach et al. 2019).

No data on potential effects on female fertility are currently available (Özdemir, 2021).

3.2.5. Other endocrine adverse events

- Glycemic alterations

  While both hyperglycemia and hypoglycemia may occur during TKI treatment, ICI therapy is responsible for diabetes mellitus in approximately 1–2 % of cases, particularly with anti-PD-1 therapy, while it is extremely rare with anti-CTLA-4 treatment (Kotwal et al. 2019; Stamatouli et al. 2018).

  The time of onset, demonstrated by elevation of blood glucose and glycated haemoglobin (HbA1c) and reduction of fasting C-peptide level, varies from 1 to 9 months after starting therapy (Chieng et al. 2022; De Filette et al., 2019a)
- Hypocalcaemia

Primary hypoparathyroidism is a very rare event during treatment with ipilimumab and nivolumab but can lead to severe symptomatic hypocalcaemia (Win et al. 2017).

3.3. Endocrine evaluation at basal, during, and at the end of first-line treatment with ICIs combinations

Endocrine toxicities from ICIs combinations can range from straightforward clinical scenarios to complex alterations, which are challenging to manage outside of specialized settings (J. B. A. G. Haanen et al. 2017; Wright et al., 2021; Schneider et al. 2021; Thompson et al. 2022; Brahmer et al. 2021). Nevertheless, unlike other adverse events, endocrine toxicities can be usually managed without withdrawal or dose reduction of ICIs treatment (Wright et al., 2021).

However, these IRAEs can persist long-term, even after drugs discontinuation, indicating a patient predisposition to endocrine diseases and potential irreversible drug-induced damage on the secreting cells.

We will discuss the suggested assessments useful to prevent and identify endocrine alterations occurring during treatment with ICIs combinations (Haanen et al. 2017).

3.3.1. Thyroid alterations

We recommend, in accordance with all available guidelines, assessing TSH and free T4 levels before starting therapy as TSH levels is predictive of the potential risk of developing thyroid dysfunction (Thompson et al. 2019; Haanen et al. 2017) (Fig. 2).

Monitoring should continue every 4–6 weeks during follow-up though intervals may vary based on baseline TSH values. In particular,

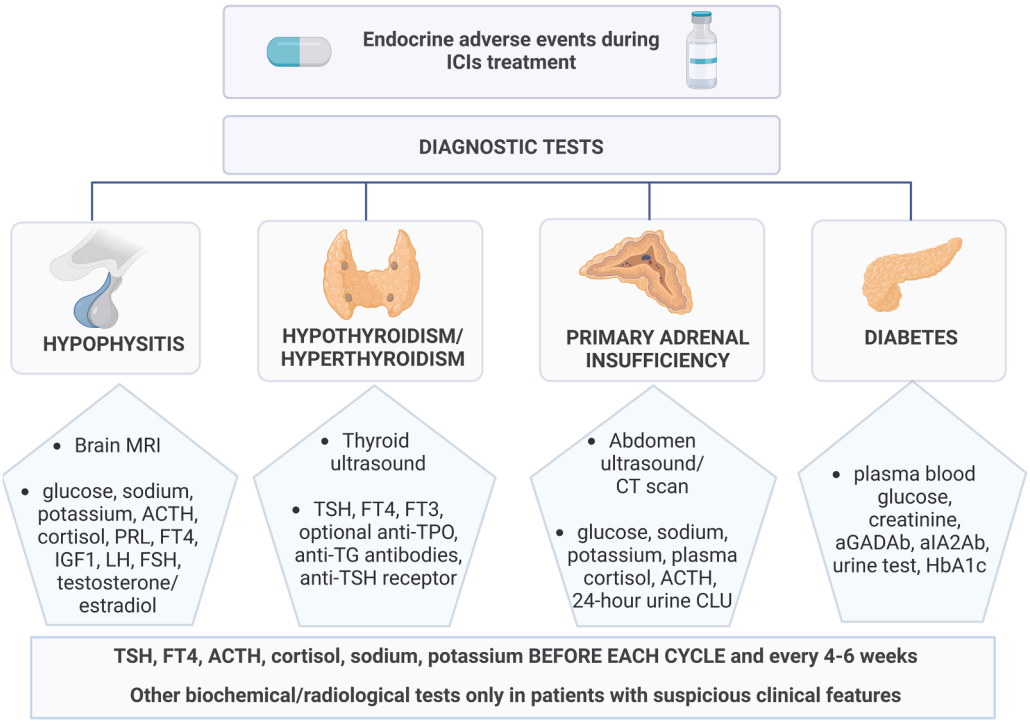

Fig. 2. Graphic illustration of the biochemical and radiological assessments required in order to investigate the main endocrine immune-related adverse events (IRAEs) during immune checkpoint inhibitors (ICIs) treatment. Created with Biorender.com. MRI, Magnetic Resonance Imaging; ACTH, adrenocorticotropic hormone; PRL, prolactin; TSH, Thyroid-stimulating hormone; FT4, Free Thyroxine; FT3, Free triiodothyronine; IGF-1, insulin-like growth factor; LH, Luteinizing hormone; FSH, follicle-stimulating hormone; anti-TPO, anti- Thyroid Peroxidase; anti-TG, anti-Thyroglobulin; CT, computed axial tomography, CLU, urinary free cortisol; aGADab, anti-glutamic acid decarboxylase antibodies; aIA2Ab, tyrosine phosphatase antibodies; HbA1c, glycated haemoglobin.

in patients with TSH < 1.7 mU/l and negative ATAbs we can revaluate thyroid function less frequently during treatment, e.g. every 3 months, unless signs or symptoms arise (Fig. 2). On the contrary, in patients with baseline TSH > 1.7 mU/l and/or positive ATAbs, TSH and FT4 levels must be periodically monitored (approximately every 2 months), considering the wide range of onset times for endocrine AEs (Brilli et al. 2021; Luongo et al. 2021; Ruggeri et al. 2023; Barlas et al. 2024).

Given the variable onset of IRAEs, biochemical investigations should be promptly performed when suspicious symptoms are present, regardless of the last assessment (Chieng et al. 2022).

3.3.2. *Pituitary evaluations*

All patients starting treatment should be assessed for fasting levels of ACTH and cortisol at 8–9 am at baseline and every 4–6 weeks during treatment. No glucocorticoids should be administered in the weeks before the biochemical evaluation (Fig. 2).

Signs or symptoms related to hypopituitarism necessitate comprehensive tests, including cortisol, ACTH, and urinary free cortisol levels from a 24-hour urine collection to exclude the presence of secondary hypoadrenalism (Fig. 2).

If central hypogonadism is suspected, luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, and estrogen should be measured and the diagnoses based on the finding of low hormone levels (Ryder et al. 2014).

Hypophysitis can rarely lead to a pan-hypopituitarism, resulting in central hypothyroidism with reduced FT4 and FT3 levels, and less frequently reduced IGF1 and prolactin levels (Rossi et al. 2024).

Magnetic Resonance Imaging (MRI) of the pituitary gland should be performed if hypophysitis is suggested by signs, symptoms, and biochemical tests (Fig. 2).

3.3.3. *Adrenal alterations*

The diagnosis of PAI can be challenging requiring regular systematic biochemical monitoring (Castinetti et al. 2019; Castinetti et al. 2018; Haissaguerre et al. 2018). The assessment requires periodic adrenal function tests since the average time of onset of PAI ranges from 2 weeks to 10 months and sometimes even after discontinuation of ICIs treatment (Atkinson and Lansdown, 2022; Paepegaey et al., 2017a; Grouthier et al. 2020).

In acute adrenal insufficiency crisis, associated with hyponatremia and hyperkalemia, plasma cortisol and ACTH values should be urgently assessed, and intravenous or oral hydrocortisone administered immediately. Plasma cortisol values > 500 nmol/L at any time of day exclude adrenal insufficiency. In the case of routine non-urgent situations, low cortisol values (often < 138 nmol/L) and elevated ACTH (often > 2 times the upper limit of normal range) confirm PAI (Fig. 2). If 8–9 a.m. cortisol values are between 138 and 500 nmol/L, a stimulation test with ACTH 250 mcg can be performed.

A cortisol level increase > 500 nmol/L (> 18.1 μg/dL or > 15 μg/dL, considering the new more sensitive cortisol assays) excludes PAI. Moreover, plasma aldosterone and renin measurements should check for mineralocorticoid deficiency, indicated by elevated renin and reduced aldosterone levels. Adrenal antibodies testing may be useful to identify cases of autoimmune PAI (Castinetti et al. 2019; Castinetti et al. 2018; Haissaguerre et al. 2018; Spagnolo et al. 2022; Paepegaey et al., 2017a).

Confirmed adrenal insufficiency requires an abdominal CT scan, if not recently performed, to exclude adrenal metastases or adrenal atrophy (F Castinetti et al. 2019b; Frédéric Castinetti et al. 2018; Haissaguerre et al. 2018; Spagnolo et al. 2022; Paepegaey et al., 2017a; Grouthier et al. 2020) (Fig. 2).

3.4. *Management of endocrine adverse events during combined ICIs combinations*

The management of endocrine adverse events induced by TKIs and ICIs requires a multidisciplinary approach, including an endocrinologist.

Diagnosis may not be easy due to changes in hormone levels during acute illness and the concurrent medications, such as narcotics or corticosteroids. Consequently, alongside baseline and follow-up biochemical evaluations, patient education and close monitoring for early signs and symptoms of endocrine dysfunction are paramount. Moreover, the clinical features of endocrine dysfunction are usually nonspecific and may overlap with concurrent illnesses. While thyroid immune-related adverse events are generally manageable, adrenal insufficiency and insulin-dependent diabetes can be life-threatening if not promptly recognized and treated (Kotwal et al. 2023). Immune-related endocrinopathies differ from other IRAEs in three main ways: (1) high-dose corticosteroids are generally not necessary; hormonal replacement therapy is effective in almost all cases; (2) ICI and TKI therapy can usually be continued; (3) endocrine deficiency is often permanent, necessitating lifelong replacement therapy (Haanen et al. 2022; Basek et al., 2023; Elshafie et al. 2024; Yang et al. 2024). Indeed, only in cases of severe thyroid eye disease or hypophysitis with headache and compression of the optic chiasm a high dose corticosteroid should be used, and interruption of ICI be considered. No other endocrine adverse events require ICI treatment interruption (Husebye et al. 2022).

First-line immunotherapy combinations for metastatic RCC, such as anti PD-1 (pembrolizumab or nivolumab) with axitinib, cabozantinib, or lenvatinib are more frequently associated with thyroid toxicities, while hypophysitis, adrenal insufficiency or diabetes are rare. However, due to the severity of these conditions if not promptly diagnosed, special attention is mandatory. The combination of nivolumab + ipilimumab is associated with higher risk of thyroid toxicities, hypophysitis and adenal insufficiency compared to ICI monotherapy (hypophysitis: 8–10 % vs 0.5–1 % with an anti-PD-1 therapy alone, adrenal insufficiency: 4–8 % vs <1 % when only one ICI is used (Bai et al., 2020; De Filette et al., 2019b).

3.4.1. *Thyroid alterations*

Differential diagnosis is crucial to target appropriate therapy. Antithyroid thionamide drugs (i.e. propylthiouracil, thiamazole, and carbimazole) are necessary only in cases of Graves' disease, not for destructive thyroiditis. These patients do not require high-dose corticosteroids, and combination treatment should be interrupted only if hyperthyroidism is severe. Thyroid eye disease requires high-dose corticosteroids, particularly if the optic nerve is compressed. ICI treatment should be held, and the decision to restart treatment should be made on a case-by-case basis since the low number of cases described has not yet allowed clear recommendations (Yu et al. 2020; Husebye et al. 2022). Thyrotoxicosis due to destructive thyroiditis can be treated with non-cardioselective beta-blockers, such as propranolol or atenolol, to relieve symptomatic peripheral effects of thyroid hormones. Beta-blockers may be discontinued when hyperthyroidism resolves or switches to hypothyroidism. Hypothyroidism is easily managed with levothyroxine. According to current guidelines, levothyroxine should be initiated when TSH is > 10 mIU/L, and/or fT4 is below the lower reference limit (Husebye et al. 2022; J. Haanen et al. 2022; Schneider et al. 2021). Levothyroxine may be considered also in patients with serum TSH between 5 and 10 mIU/l and positive TPO antibodies (F Castinetti et al. 2019b). In cases of serum fT4 below the lower reference limit and normal TSH, central hypothyroidism should be recognized, and concurrent hypoadrenalism should be ruled out before starting levothyroxine treatment. Levothyroxine treatment may precipitate an adrenal crisis if glucocorticoid replacement therapy is not initiated in patients with adrenal insufficiency (Fig. 3). The recommended starting dose of levothyroxine is 1.0 mcg/kg/day, but higher doses, up to 1.6 mcg/kg/day, may be necessary in patients with overt hypothyroidism to achieve a euthyroid state (Tsai et al. 2024). Lower doses may be considered in older patients or in those with concomitant cardiovascular disease. Hypothyroidism caused by ICI treatment is generally permanent. However, patients developing hypothyroidism because of TKI treatment may attempt to discontinue levothyroxine treatment. Patients developing thyroiditis and hypothyroidism can safely continue combination treatment with both ICI and TKI.

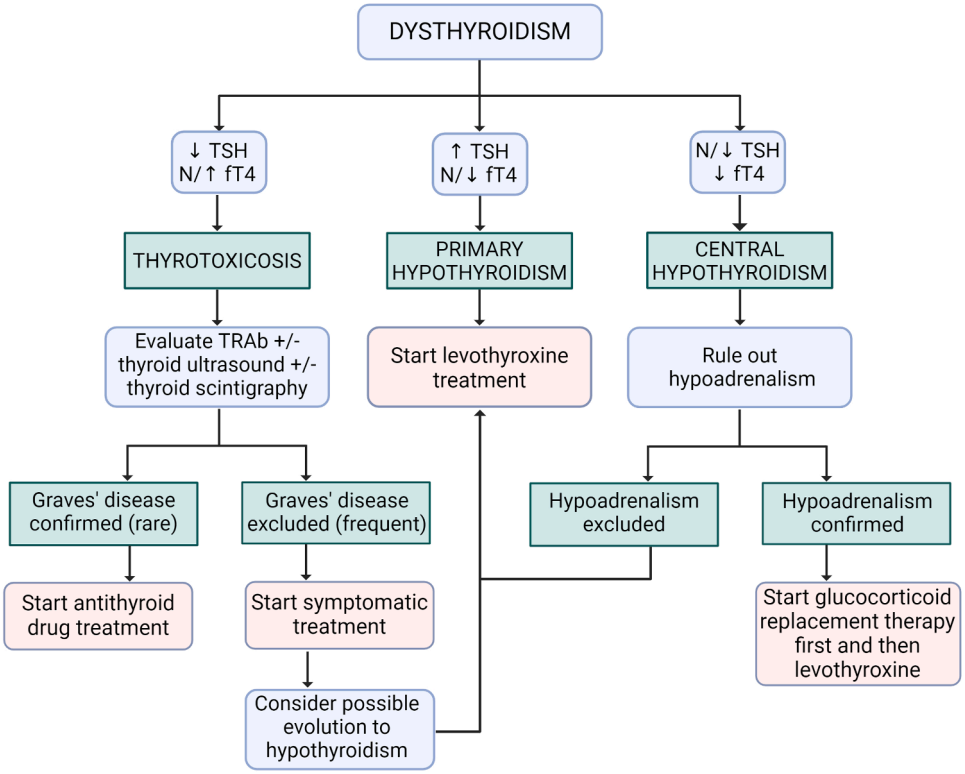

Fig. 3. Flowchart about management of thyroid alterations during combined ICI + TKI treatment. Created with Biorender.com.

3.4.2. Pituitary alterations

Treatment should not be delayed, especially if an adrenal crisis is suspected. In this situation, serum cortisol and ACTH levels should not postpone treatment, as this can be fatal.

Although adrenal insufficiency is a rare occurrence, its severity makes it essential to first assess serum levels of ACTH and cortisol. These levels help determine whether the condition can be related to primary or secondary adrenal insufficiency. If the findings suggest a secondary adrenal insufficiency, it will be necessary to evaluate also levels of other pituitary hormones **(**Fig. 5**).**

For adrenal crisis, immediate parenteral injection of 100 mg hydrocortisone should be initiated, followed by appropriate fluid resuscitation and 200 mg of hydrocortisone every 24 hours (via continuous IV therapy or 6-hourly injection) (Bornstein et al. 2016). High-dose glucocorticoids should also be used in cases of hypophysitis with optic chiasm compression or other severe compressive symptoms (such as compromised vision or untreatable headache). In other situations, hypophysitis is safely managed with hormonal replacement therapy and it has been reported that patients receiving high-dose glucocorticoids may have reduced survival (Albarel et al., 2015; Faje et al. 2018). Glucocorticoid replacement therapy consists of 15–25 mg hydrocortisone (or cortisone acetate 20–30 mg daily) divided into two or three administrations. Prednisolone at a dose of 3–4 mg/day is an alternative (Smith et al. 2017); whereas dexamethasone is not recommended. Recovery from ACTH deficiency is rare, but if glucocorticoids are supposed to be stopped, they should be slowly tapered, and pituitary-adrenal axes should be assessed with ACTH stimulation test. Patients should be educated on preventing adrenal crises by adjusting glucocorticoid treatment in case of illness, vomit, trauma, or surgical interventions (sick day rules). It is advisable for patients to wear a medical alert bracelet or necklace and carry a steroid emergency card to communicate appropriate management in case of an adrenal crisis (Bornstein et al. 2016; Husebye et al. 2022). Central hypothyroidism is safely managed with levothyroxine replacement therapy; however, adrenal insufficiency must always be ruled out before starting levothyroxine treatment. Hypothyroidism may recover if ICI treatment is stopped; therefore, treatment may be tapered and reduced, especially if low doses of levothyroxine are used (Min et al. 2015). If persistent, hypogonadotropic hypogonadism may be managed with testosterone in men and estrogen and progestogen in women of reproductive age, unless the patient has a poor oncological prognosis. The rationale for sex steroid replacement therapy is to maintain patients' well-being, reduce the risk of osteoporosis and cardiovascular disease, and in men, anemia and muscle weakness as well. In women, transdermal estrogen administration may reduce the thromboembolic risk and should be preferred (Husebye et al. 2022). Finally, albeit rare, diabetes insipidus presenting with polyuria and dehydration is confirmed by hypernatremia, high serum osmolality, and dilute urine with low specific gravity. Endocrinological evaluation is needed to confirm diagnosis and to start desmopressin treatment. GH deficiency during ICI+TKI treatment has been reported, but GH replacement therapy during malignancy is contraindicated (Fleseriu et al. 2016).

3.4.3. Adrenal alterations

In cases with suspected adrenal insufficiency, it is crucial to first assess serum levels of ACTH and cortisol. If the values are consistent with primary adrenal insufficiency (usually high ACTH levels and normal or low cortisol levels), an appropriate replacement therapy should be warranted **(**Fig. 5**).**

In particular, adrenal insufficiency is managed with glucocorticoid replacement therapy, similar to central hypoadrenalism (Bornstein et al. 2016; Husebye et al. 2022). In patients with confirmed PAI, unlike secondary cases (caused by pituitary or hypothalamic imbalance), mineralocorticoid replacement therapy should be initiated, with fludrocortisone at a dose of 0.05–0.15 mg/day, while avoiding a low-sodium diet. If prednisolone is used for glucocorticoid replacement therapy, patients should receive a slightly higher mineralocorticoid dose (0.05 mg/day) since prednisolone lacks any mineralocorticoid effect, unlike hydrocortisone and cortisone acetate.

3.4.4. Glycaemia alterations

Unlike hyperglycemia induced by TKIs, diabetes mellitus caused by ICIs often presents with diabetic ketoacidosis (DKA). Management varies according to the severity of hyperglycemia and the etiology of diabetes. In cases of DKA, intravenous insulin and fluid resuscitation must be promptly initiated (Tran et al. 2017). In ICI-induced diabetes, subcutaneous insulin with a basal-bolus regimen is recommended due to islet destruction. In TKI-induced hyperglycemia, metformin should be used as first-line treatment, and subsequent treatment should follow classic guidelines for non-iatrogenic diabetes (Fig. 4). A reasonable HbA1c target is < 8 %, but it should be adjusted according to the oncological and patient's situation (Buffier et al. 2018). Some TKIs, such as axitinib, may be responsible for hypoglycemia (Mugiya et al. 2024). Patients should be prepared to manage a hypoglycemic crisis and, if they are under diabetic treatment (for pre-TKI diabetes), glucose self-monitoring should be implemented, drugs that can cause hypoglycemia (such as sulphonylureas) should be avoided, and antidiabetic drug doses adapted to the glycemic situation under TKI treatment. High-dose glucocorticoids for the treatment of ICI-induced diabetes mellitus are not recommended, as they not only do not preserve beta cell function but also worsen hyperglycemia (Husebye et al. 2022) Fig. 5.

4. Conclusion

This study aims to assist clinicians rapidly manage the most common endocrinological side effects associated with first-line treatment of advanced RCC. It is based on the expertise of endocrinology and oncology professionals. Expertise in managing immune-related adverse events during therapy with ICIs enables oncologists prevent drug dosage reductions or interruptions that may negatively impact oncological outcomes.

In cases of severe or rare IRAEs, effective collaboration within a multidisciplinary team is critical to the efficiency and holisticity of the patient care process.

Critical view section

We are witnessing an unprecedent time in the advanced renal carcinoma therapeutic landscape. The recent mRCC paradigm shift is the result of a more accurate knowledge of biological mechanisms behind neoplastic development and progression. RCC is often associated with abnormalities of the von Hippel-Lindau (*VHL*) tumor suppressor gene, ultimately resulting in dysregulation of angiogenic pathway. In addition, we known that a key feature of RCC is its immunogenicity. Consequently, there is a strong rationale in the use of the combination of two immunotherapy agents or two drugs with distinct mechanisms of action, ICIs in association with TKIs.

These drugs, synergistically counteract the main mechanisms that promote mRCC tumor development and growth: angiogenesis and the immune evasion process.

While ICIs attempt to reawaken exhausted immune cells in their innate fight against tumor cells, anti-angiogenics can restore the vasculature in the tumor micro-environment, enhancing the potential of infiltration of effector immune cells and thereby increasing therapy efficacy (Delcuratolo et al. 2023).

Several phase III studies explored the efficacy of immunotherapy-based combinations in the mRCC first-line treatment and demonstrated the ability to provide unprecedented response rates and improved survival in the metastatic setting, compared with TKI monotherapy (Albiges et al. 2020; Delcuratolo et al. 2023; Plimack et al. 2023; Motzer et al. 2022; Rizzo et al. 2022).

With several treatment options and the lack of predictive

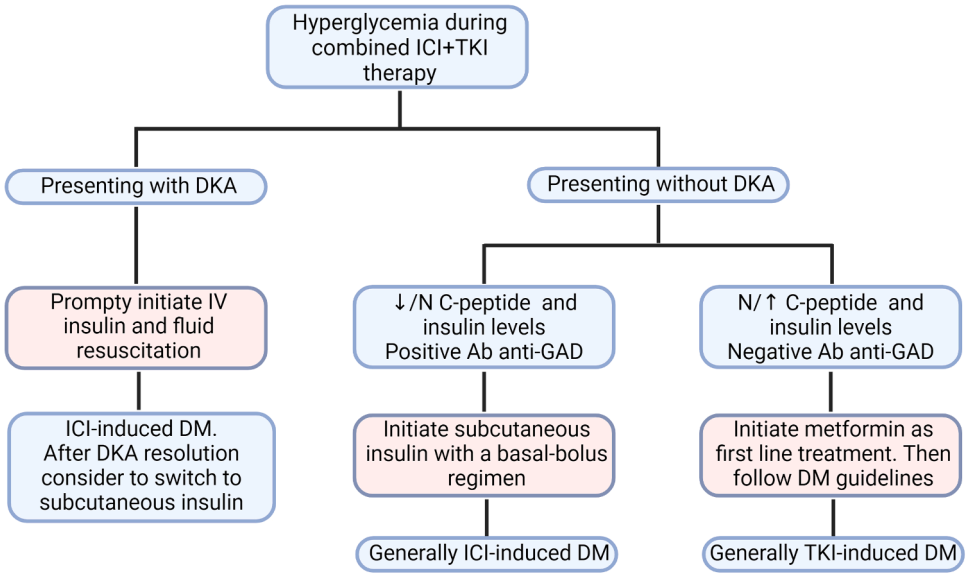

Fig. 4. Flowchart about management of hyperglycemia during combined ICI + TKI treatment. Created with Biorender.com.

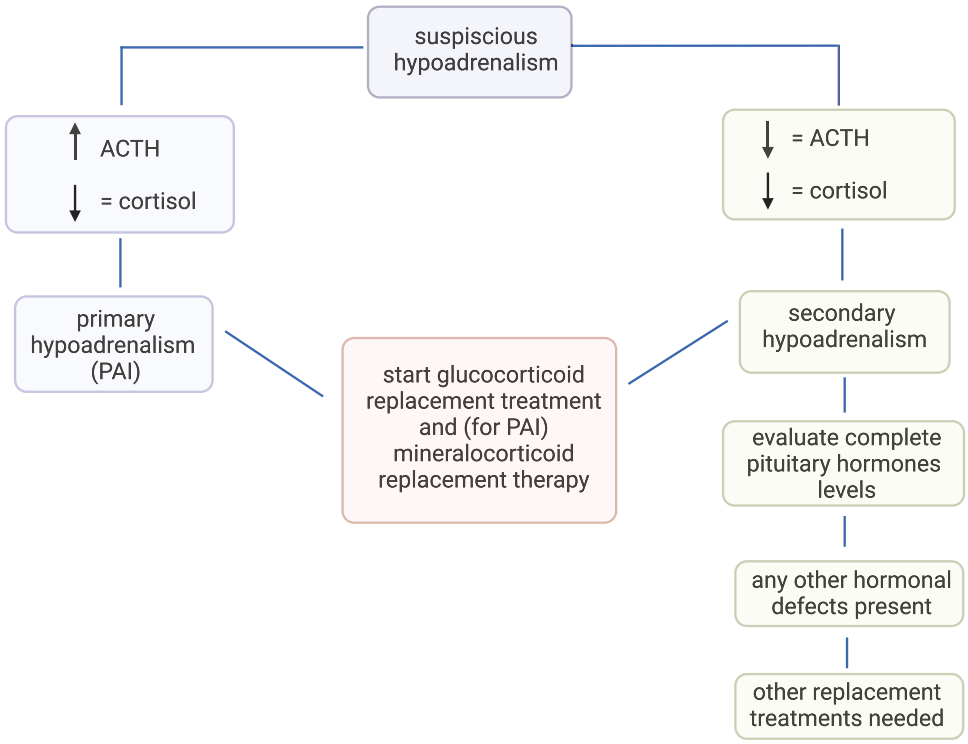

Fig. 5. Flowchart about management of suspicious primary and secondary hypoadrenalism during combined ICI + TKI treatment. Created with Biorender.com.

biomarkers, the choice of the best first line regimen for each patient is a critical challenge.

Clinicians should consider clinical factors to determine who may benefit from one treatment over another.

We identified two risk scores taking into account known predictors factors of survival: Memorial Sloan-Kettering Cancer Center (MSKCC) and the International Metastatic RCC Database Consortium (IMDC).

If none of the factors are present, the disease has a favorable prognosis, an intermediate prognosis if one to two are present, and a poor prognosis if more than three are present (Delcuratolo et al. 2023).

Selection of the best treatment for each patient is not the only challenge in mRCC first line therapy. In fact, despite significant progress made with the use of multiple drugs in combination, in our opinion, it is crucial to underline the need of successfully preventing and counteracting side effects. This is the only way to ensure a good quality of life for patients along the course of treatment and, as a result, a successful treatment, keeping in mind that the occurrence of adverse events is the primary reason for drug discontinuation and dose reduction.

A deep understanding of prevention and management of toxicity due to immunotherapy combinations is crucial to ensure therapy efficacy. In particular, it has great relevance to oncologist to learn how to better manage the easier endocrinological toxicities and when the clinical case need multidisciplinary discussion. In addition, it is often difficult to identify which agent of the therapeutic combinations is responsible for

each specific toxicity. In this review we analyse the evidence about endocrine adverse events of immunotherapy combinations in mRCC, focusing on their prevalence, prevention and management.

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CRediT authorship contribution statement

Carla Colombo: Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing. Simone De Leo: Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing. Ilaria Campisi: Resources, Data curation, Writing- review & editing. Erica Palesandro: Resources, Data curation. Fabio Turco: Resources, Data curation. Consuelo Buttigliero: Writing – review & editing. Laura Fugazzola: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. Marcello Tucci: Conceptualization, Methodology, Writing – original draft, Writing – review & editing

Declaration of Competing Interest

No conflict.

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