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REVIEWS

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Steroidogenesis inhibitors in the treatment of nonoperative Cushing's syndrome – a literature review

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary **Background.** Cushing's syndrome (CS) is a disorder caused by excess cortisol production. It is three times more often seen in female than male patients, and overall, it is observed in 2–3 per million/year. In nearly 70% of cases, this is due to a pituitary tumour secreting adrenocorticotropic hormones. The first-line approach to treat these cases is the surgical removal of the tumour. However, in nearly a quarter of cases, this proves ineffective. These patients should be then treated with pharmacotherapy, while untreated CS may be lethal. The most numerous groups of pharmaceutics in CS treatment are steroidogenesis inhibitors.

Objectives. The purpose of this article is to review the latest publications from 2015 to 2022, which state the medical approach with steroidogenesis inhibitors to inoperative CS, the advantages, as well potential burdens and adverse effects of this pharmacological treatment.

Material and methods. A review of literature regarding adrenal steroidogenesis inhibitors was performed using the PubMed database; the search terms Cushing's syndrome, inoperative, ketoconazole, levoketoconazole, metyrapone, mitotane, etomidate, and osilodrostat were applied.

Results and conclusions. This review states the current data pertaining to the effectiveness of hypercortisolaemia treatment, as well as the potential adverse effects of ketoconazole, levoketoconazole, metyrapone, mitotane, etomidate, osilodrostat – steroidogenesis inhibitors currently used in the therapy of nonoperative Cushing's syndrome.

Key words: pituitary ACTH hypersecretion, Cushing syndrome, steroids, review.

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Background

Cushing's syndrome (CS) is a set of clinical symptoms and hormonal imbalances due to elevated levels of glucocorticosteroids in plasma. This can be of endogenous origin (0.7–2.4 per million population per year), both in adrenocorticotropic hormone (ACTH)-dependent and ACTH-independent types. ACTH-dependent CS (75–80% of endogenous CS) is diagnosed in patients with ACTH-secreting or corticotropin-releasing hormone (CRH)-secreting tumours. When the tumour is located specifically in the pituitary gland, Cushing's disease (CD) is diagnosed. ACTH-independent CS (15–20% of endogenous CS) is diagnosed when an adrenal tumour, carcinoma or macronodular hyperplasia (AIMAH) are the cause [1, 2].

First-line therapy for patients diagnosed with CD is an operative approach – transsphenoidal pituitary surgery both microscopic and endoscopic. However, in nearly 20% of patients, this proves ineffective [3]. These patients should be treated with pharmaceutics, since untreated CD increases mortality and impairs health-related quality of life (HRQoL) [2].

Pharmacological treatment

CS should be treated according to its cause. Surgery is the first-line treatment for endogenous CS; however, if this proves ineffective or impossible to conduct, medical treatment is a second-line option. Pharmacological therapy includes different types of drugs: steroid synthesis inhibitors (ketoconazole, levoketoconazole, metyrapone, mitotane, etomidate, osilodrostat); somatostatin analogues (pasireotide); dopamine agonists (cabergoline); glucocorticoid receptor antagonists (mifepristone) [4].

Steroidogenesis inhibitors

Six steroidogenesis inhibitors are available in the treatment of CS. Ketoconazole and metyrapone have been used for some time now. Novel drugs introduced into treatment are levoketoconazole and osilodrostat [5–7]. Mitotane is mostly used in the treatment of adrenocortical carcinoma and etomidate is present in severe cases of CS when oral medications cannot be used [8, 9].

Ketoconazole

Ketoconazole is a European Medicines Agency (EMA)-approved antifungal imidazole agent that inhibits multiple steps involved in adrenal steroidogenesis. (Figure 1). It is administered daily at dosages of 200–1,200 milligrams per 24 hours two or three times a day due to its short half-life (3.3 hours) [10]. In the largest multicentre study, 200 patients with CD received ketoconazole (median dose 600 milligrams daily) that induced remission in 64.7% of patients treated for more than 24 months [11]. During ketoconazole treatment, improvements in clinical symptoms such as body weight, blood pressure, glycaemia, kalaemia, as well as hirsutism and menstrual cycles in women, were observed (Table 1) [12]. However, in men ketoconazole impaired testicular androgen production, leading to hypogonadism [13]. In addition to a headache, dermatological symptoms (pruritus, skin rash) were observed [6]. Other adverse effects such as liver enzymes elevation, gastrointestinal disturbances and adrenal insufficiency occurred in some patients [5, 14]. On this basis, the EMA recommends not to initiate treatment with ketoconazole in patients who present two times the upper the limit of normal liver enzymes. When the patient undergoes ketoconazole treatment, it is advised by the EMA to check the liver enzymes weekly for the first month of treatment or after a dose increase, and then it can be performed monthly for 6 months [15]. Moreover, ketoconazole absorption is impaired in patients taking proton pump inhibitors or those with achlorhydria, since ketoconazole requires an acid gastric environment to be absorbed [16]. Ketoconazole has a great number of drug interactions because of the inhibition of cytochrome P3A4 – (CYP3A4). On this ground, physicians should review all other medications concurrently taken by patients, especially those that inhibit CYP3A4 (itraconazole, clarithromycin, ritonavir and others), as well as those that induce CYP3A4 (rifampin, carbamazepine, phenytoin and others), so as not to interfere with ketoconazole treatment [6]. Ketoconazole also has a slower onset of action than metyrapone. Taking this into consideration, as well as the drug interactions of ketoconazole, metyrapone is preferable in the treatment of CS [16].

Levoketoconazole

Levoketoconazole is a 2S, 4R enantiomer of ketoconazole and blocks the same steroidogenic enzymes (Figure 1) [18]. At present, there are no official EMA recommendations regarding the use of levoketoconazole in the treatment of nonoperative Cushing's syndrome. Levoketoconazole is administered twice a day at dosages of 300–1,200 milligrams/day and shows a longer half-life than ketoconazole (4–6 h) [19]. The less frequent daily dosage of levoketoconazole in comparison to ketoconazole appeared promising when it came to hepatotoxic adverse effects; however, phase III studies did not confirm that levoketoconazole had a better impact on liver enzyme rates in comparison to ketoconazole, as both drugs induce elevation of liver enzymes (AST – aspartate aminotransferase and ALT – alanine aminotransferase). The phase III, double-blinded, multicentre study LOGICS has however shown that levoketoconazole induced a significant decrease (normalisation) in mean urinary free cortisol (mUFC) in 50% of patients at the end of randomised withdrawal, whilst a placebo brought normalisation only in 4.5% of patients. Therefore, the data stated in a phase III, open-label, multicentre clinical trial (SONICS study) were confirmed.

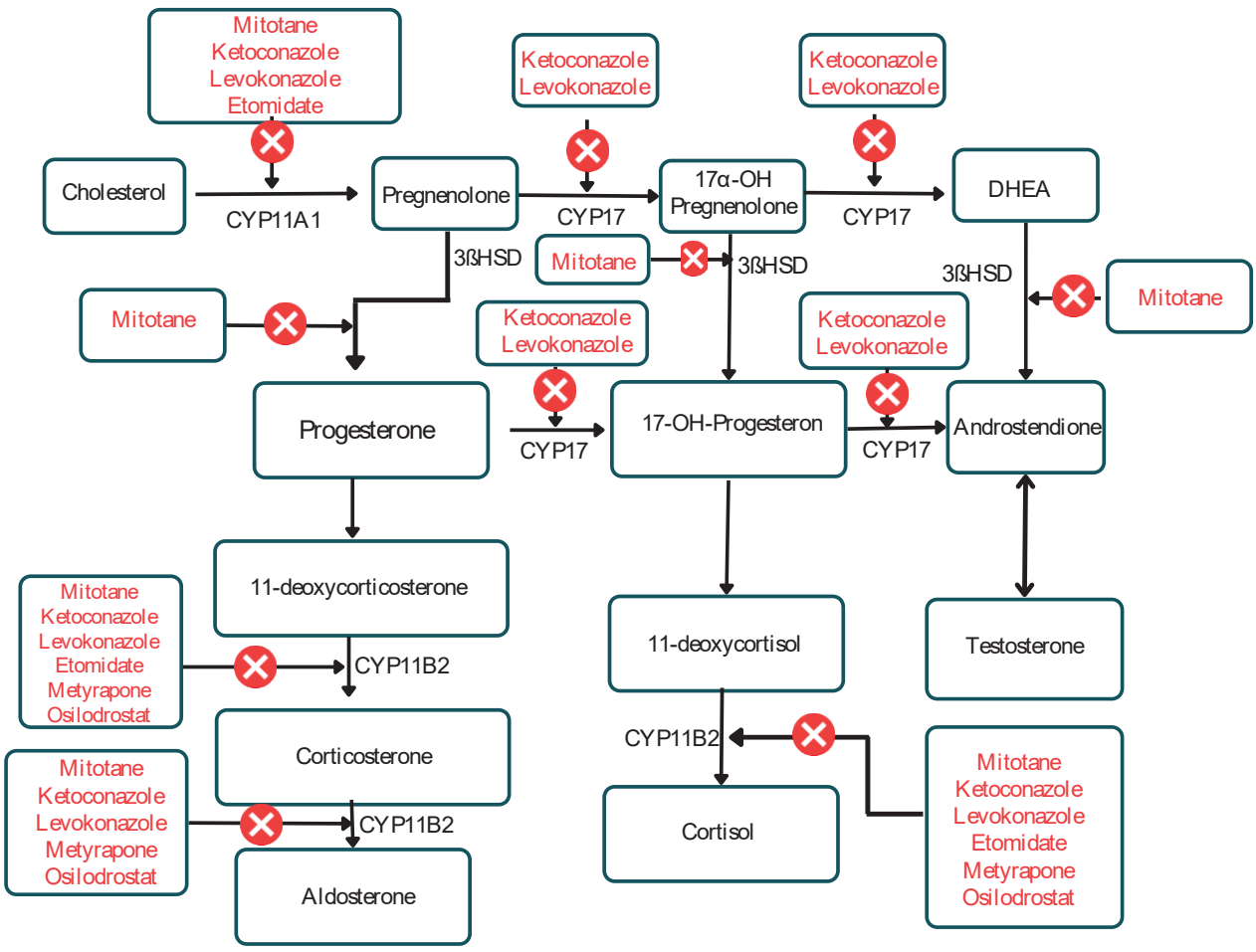

Figure 1. Steroidogenesis in the adrenal cortex and inhibition of its specific pathways by steroidogenesis inhibitors

(17α-OH – 17α-hydroxylase; 17-OH – 17-hydroxylase; 3βHSD – 3β-hydroxysteroid dehydrogenase; CYP – cytochrome) [6, 7, 17]

What was also observed in both studies was a significant decrease in glycated haemoglobin, both in diabetic and nondiabetic patients. Levoketoconazole administration brought about improvement of clinical traits in aspects such as body weight, glycaemia, lipidaemia, acne and hirsutism withdrawal in women (Table 1). The adverse effects observed with levoketoconazole were mainly nausea in ~ 30% of patients, headache in ~ 25% of patients, hypokalaemia in ~ 26% of patients, and hypertension in ~ 20% of patients [20–22].

Metyrapone

Metyrapone is a steroidogenesis inhibitor acting mainly against CYP11B2 (Figure 1), it is approved by the EMA for the treatment of CS with its daily dosage of 500–6,000 milligrams/day. It has a short half-life (2 hours) and requires administration 4–6 times a day; however, it may be the fastest-acting agent in terms of cortisol secretion. Possible adverse effects (glucocorticoid, mineralocorticoid and adrenal androgens overproduction) occur since metyrapone induces a compensatory rise in ACTH levels due to its efficient cortisol synthesis inhibition [17]. The first multicentre prospective study PROMPT, conducted on 50 CS patients, showed that metyrapone, at week 12, induced remission (based on mUFC levels) in 47% of patients [23]. In another retrospective study conducted on 91 patients with CS, psychic symptoms, glycaemia and hypertension improved in over 70% of those examined [24]. Treatment with metyrapone brought about improvement in clinical symptoms of CS (body weight, hypertension, glycaemia, lipidaemia) [25]. Literature states a case where metyrapone was used in the treatment of CS during pregnancy with promising results – with maternal serum and saliva cortisol levels in the upper half of the normal pregnancy range. The pregnancy ended with the delivery of a healthy male infant who presented a low cortisol level – 5 nanomoles per litre (nmol/L) on the first day of life, without clinical symptoms of adrenal insufficiency [26]. The most frequent adverse effects stated in literature were hirsutism and acne in women (up to 70% of female patients), and hypertension (up to 48%), dizziness, nausea, oedema and hypokalaemia were reported in different studies (Table 1) [12, 23, 27].

Mitotane

Mitotane is approved by EMA in cases of adrenocortical carcinoma, but it may sometimes be used to treat severe hypercortisolaemia [17]. The types of cytochromes that it inhibits were stated in Figure 1. The daily dose of mitotane is determined by its level in serum; optimally it should be within 14 up to 20 milligrams per litre, measured every 2 weeks until the maintenance dose is settled. Usually, the initial dose of mitotane is 2–3 grams per day, gradually increasing until the expected level in serum is obtained. When the maintenance dose is reached, the mitotane level in the serum should be measured monthly [28]. Retrospective analysis of 76 patients treated with mitotane stated that remission of hypercortisolaemia was achieved in 48 of the 67 patients (i.e. in 72% of those examined) after a median time of 6.7 months. However, after treatment discontinuation, recurrence of hypercortisolism was noted in 17 of 24 patients (i.e. in 71% of those examined) after a median time of 13.2 months [9]. In another study, mitotane was examined as adjuvant therapy for the surgical treatment of adrenocortical carcinoma. In the first year of follow-up, no recurrence of hypercortisolaemia was detected, and 6 patients (37%) presented with a recurrence after 15–24 months. During the treatment, the most common adverse effects were hepatotoxicity (transaminitis) hypoadrenalism, nausea or vomiting and general fatigue (Table 1) [29].

Etomidate

Etomidate is a drug used in anaesthesiology to induce general anaesthesia and is approved by the EMA only for this indication [30]. The types of cytochromes that it inhibits were stated in Figure 1. It is used in patients with hypercortisolaemia who cannot use oral treatment – etomidate is intravenously ad-

Table 1. Summary of the most important advantages and disadvantages or adverse effects of steroid inhibitors used in the treatment of nonoperative Cushing's syndrome

Drug	Advantages	Disadvantages / adverse effects
Ketoconazole	• normalise UFC in 50% of patients retrospectively • improves body weight, blood pressure, glycaemia, kalaemia • decreases hirsutism • regulates menstrual cycles	• impairs testicular androgen production • indicates pruritus and skin rash • hepatotoxicity • number of drug interactions • slower onset of action
Levoketoconazole	• normalise UFC in 31% of patients prospectively at 6 months • decreases glycated haemoglobin • improves body weight, lipidaemia • acne, hirsutism withdrawal in women	• nausea • headache • hypertension • hypokalaemia
Metyrapone	• normalise UFC in 47% retrospectively • fastest-acting agent in terms of cortisol secretion • possible use during pregnancy	• may indicate glucocorticoid, mineralocorticoid and adrenal androgen overproduction • hirsutism and acne in women • hypertension • dizziness • nausea, oedema • hypokalaemia
Mitotane	• used in cases of adrenocortical carcinoma	• hepatotoxicity (transaminitis) • hypoadrenalism • nausea, vomiting • general fatigue
Etomidate	• the only drug admitted intravenously with rapid onset of action	• hypersomnia • low blood pressure • nausea, vomiting • reported cases of adrenal insufficiency
Osilodrostat	• improvements – body weight, physical symptoms • decrease in fasting plasma glucose, blood pressure	• hypokalaemia • QTc prolongation • hypertension • secondary amenorrhea, hirsutism, acne in women

ministrated [31]. Cortisol production is inhibited with a dose of 2.5 milligrams per hour of etomidate [32]. Etomidate presents a rapid onset of action – within 11 hours of infusion, a significant decrease in cortisolaemia is achieved [33]. As an anaesthetic drug, etomidate presents adverse effects such as hypersomnia, low blood pressure, nausea and vomiting. Adrenal insufficiency has also been observed, which may require glucocorticoid replacement (Table 1) [34].

Osilodrostat

Osilodrostat was approved by the EMA in 2020 for the treatment of endogenous CS. It inhibits CYP11B2 and CYP11B1 (Figure 1) [35]. The initial dose is 4 milligrams a day. The dose may be increased gradually (initially by 1 or 2 milligrams) based on individual response and tolerability to achieve cortisolaemia within the normal range. The maximum dose of osilodrostat is 30 milligrams twice a day [36]. In the phase III study on osilodrostat, 53% (72 out of 153) of patients achieved mUFC normalisation after 24 weeks of treatment. During the withdrawal phase, nearly 86% of patients on osilodrostat achieved normal mUFC in comparison to 29% of patients that were on a placebo [37]. Most of the patients on osilodrostat achieved improvements in parameters such as body weight (buffalo hump decrease was observed in 50%, moon face in 25%), fasting plasma glucose and blood pressure [38]. Potential adverse effects while on osilodrostat are hypokalaemia, QTc prolongation and hypertension – those parameters should be frequently monitored. In women, it is advised to also monitor androgen levels – while on osilodrostat, testosterone may be elevated, which leads to secondary amenorrhea, hirsutism and acne. These symptoms are. However, reported to be transient (Table 1) [39].

Combined therapy

Literature states several studies where combined therapy using steroidogenesis inhibitors was performed. One study describes a rapid improvement considering mUFC after 48 hours of therapy using ketoconazole (400–1,200 milligrams/24 hours), metyrapone (3.0–4.5 grams/24 hours) and mitotane (3.0–5.0 grams/24 hours) in 11 patients with severe hypercortisolism [40]. Another used ketoconazole-metyrapone (200–250 milligrams) combined therapy to treat patients with severe CS (14 had an ectopic ACTH-secreting tumour; 8 had adrenocortical carcinoma), which showed success in 73% of patients with an ectopic ACTH-secreting tumour and in 86% of patients with adrenocortical carcinoma [41]. Literature states a single case in which combined therapy using ketoconazole (dose 600 milligrams/day) and osilodrostat (30 milligrams/day) was used to treat a 53-year-old male with ACTH-independent CS. This combination was reported to be highly effective in terms of cortisol secretion – serum cortisol decreased from 660 (nmol/L) to 436 (nmol/L). Additionally, lower doses than those applied in monotherapy were used, which minimised the adverse effects previously observed in a single therapy [42].

Conclusions

Steroidogenesis inhibitors play an important role in the treatment of nonoperative Cushing's syndrome. The character of this disease and its treatment makes it crucial to monitor cortisolaemia, as well as other parameters (the concentration of some pharmaceutics in blood serum, ALT, AST, GGTP, glycaemia, lipidaemia and blood pressure) on a regular basis to achieve the expected outcomes. In addition, a progression of the disease or an occurrence of potential adverse effects should be diagnosed early and the medications adequately altered to avoid disruptive implications of uncontrolled CS.

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