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Approach to the Patient

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Approach to the Patient Treated with Steroidogenesis Inhibitors

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Abstract

Steroidogenesis inhibitors can be given to control the hypercortisolism of Cushing's syndrome in various situations: when surgery has been unsuccessful or not possible; in metastatic adrenocorticotropin hormone (ACTH) or cortisol-secreting tumors; when waiting for the maximal efficacy of radiation techniques; for rapid treatment of severe hypercortisolism in patients with occult ACTH-producing tumors; or as a presurgical treatment in patients with severe comorbidities. Whilst biochemical "control" can be achieved in more than 50% of cases, daily management of such drugs can be challenging. Indeed, with a "dose-titration" or a "block and replace" approach, defining eucortisolism is usually difficult, requiring the measurement of several biological markers. Moreover, each drug has its own side effects, which must be monitored closely. The aim of this "approach to the patient" is to shed light on the management of hypercortisolism with 4 steroidogenesis inhibitors (ketoconazole, levoketoconazole, metyrapone, osilodrostat) to help endocrinologists dealing with patients with Cushing's syndrome. Various points will be discussed, such as initial dose of treatment, dose schedule, monitoring of efficacy, and side effects of monotherapy. The combination of steroidogenesis inhibitors will also be discussed.

Key Words: Cushing's syndrome, Cushing's disease, ectopic ACTH secretion, ketoconazole, osilodrostat, metyrapone, levoketoconazole

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Clinical Case

Ms L.A., 33 years old, was diagnosed with ACTH-dependent Cushing's syndrome (CS) 2 years ago. At diagnosis, she presented with hypertension (150/90 mm Hg) and irregular menses with mild hyperandrogenism. Initial clinical evaluation found weight gain (+4 kgs during the last 6 months, body mass index 27.4 kg/m2), easy bruising for almost 3 years, and purple abdominal striae. She was not taking any medication. Laboratory evaluation showed a 2-fold increased mean late-night salivary cortisol (LNSC) (2 samples measured at 11:30 PM and midnight, on 2 consecutive days) and a 1.5-fold increased mean of 2 samples of 24-hour urinary free cortisol (24h-UFC). Serum cortisol was 102 nmol/l (3.6 ug/dL) at 8:00 AM after a 1 mg dexamethasone dose at 11:00 PM. As plasma adrenocorticotropin hormone (ACTH) was unsuppressed, at 60 and 70 pg/ml (normal range 10–60), further evaluation for ACTH-dependent CS included a corticotropin releasing hormone (CRH) test (with a 200% increase in plasma ACTH 30 minutes after injection of 100 mcg human CRH), and desmopressin test (discordant with CRH results: no plasma ACTH increase, as seen in up to 20% of Cushing's disease [CD] cases). Chest computerized tomography (CT) was unremarkable. Pituitary magnetic resonance imaging (MRI) showed a 6-mm right-sided intrasellar pituitary lesion with possible cavernous sinus invasion. Given the results of the MRI, the negative CT and the response to CRH, CD was the most likely etiology. At transsphenoidal surgery a microadenoma was resected, but possible invasion of the right cavernous sinus was noted; pathology was consistent with a corticotroph adenoma with immunoreactivity for ACTH.

As the immediate postoperative serum cortisol level was 10 nmol/l (0.36 ug/dL), she was treated with hydrocortisone 40 mg/day, which was progressively decreased to 20 mg/day over 3 months. One year after surgery her hypertension and Cushingoid physical features had resolved fully, and an 8:00 AM serum cortisol measured prior to her morning hydrocortisone dose was 500 nmol/l (18 ug/dL); hydrocortisone was stopped. A 1 mg overnight dexamethasone suppression test showed a serum cortisol of 25 nmol/l (0.9 µg/dl) (normal < 50 nmol/L–1.8 µg/dl). She was followed regularly, and 2 years later she complained of weight gain and easy bruising. Clinical examination revealed hypertension (155/95 mm Hg) and reappearance of irregular menses with moderate hyperandrogenism. Laboratory evaluation showed mild hypokalemia, 2-fold increased late night salivary cortisol (LNSC) and 1.5-fold increased mean of 2 measurements of urinary free cortisol (UFC). Morning serum cortisol was 98 nmol/l (3.5 µg/dl) after 1 mg dexamethasone the previous evening. Thus, a diagnosis of recurrent CD was established by clinical and biochemical criteria. Pituitary MRI was negative, and stereotactic whole-sellar radiation was not considered because of her age and the risk of panhypopituitarism. As the neurosurgeon felt that repeat pituitary surgery was unlikely to cure the patient, and the patient did not want to have medical therapy involving injections, medical treatment was proposed using a steroidogenesis inhibitor to reduce cortisol levels.

Rationale for the Use of Steroidogenesis Inhibitors for the Treatment of ACTH-dependent CS

Surgical resection of the lesion(s) producing ACTH is the optimal approach to treatment (1). However, if this is not possible or successful, or as in the case above, if CD recurs, second-line treatments are required (1–4). Steroidogenesis inhibitors act by inhibiting 1 or more enzymes required for cortisol synthesis (4, 5). They may be given as monotherapy, but if this is not effective, dual therapy may be needed. If steroidogenesis inhibitors are the only treatment, they must be continued until more definitive therapy is given. Alternatively, these inhibitors may be used in conjunction with radiotherapy, with intermittent withdrawal either yearly and/or when signs of adrenal insufficiency appear, to assess if the radiation has been effective (6). Of note, none of these have any tumor-directed effects which is a potential limitation of their actions in CD.

Summary of the Main Characteristics of Currently Available Steroidogenesis Inhibitors

Six steroidogenesis inhibitors are now available in different areas of the world. Some have been used for decades (ketoconazole and metyrapone) (7, 8), while use of others are more recently reported in phase 3 studies (levoketoconazole and osilodrostat) (9, 10). Here, we will not discuss the use of either mitotane, one of the major treatments of adrenocortical carcinoma that is very rarely used in benign CS (11), or etomidate, which is reserved for severe cases of CS when oral medications cannot be given (12). We will thus focus specifically on the possible use of ketoconazole, levoketoconazole, metyrapone, and osilodrostat in this patient. As a recent review (4) detailed the main mechanisms of action of these 4 drugs, we only briefly summarize their characteristics in the following paragraphs and Table 1. Each has similar efficacy as monotherapy to normalize urine cortisol secretion and any can cause adrenal insufficiency.

Table 1. Main characteristics of the steroidogenesis inhibitors ketoconazole, levoketoconazole, metyrapone, and osilodrostat

Name	Regulatory Approval	Enzymes Affected	Plasma t Half Life (Hours)	Normal UFC (% of Cases)/ Type of Study	Main Side Effects	Other Considerations
Ketoconazole	EMA; off-label in US	CYP11A1 CYP17 CYP11B2 CYP11B1	1–3 (up to 10)	50%/retrospective	Increased liver enzymes in 10–15% cases	Decreased testosterone → male hypogonadism; stimulates CYP3A4 → drug–drug interactions
Levoketoconazole	Investigational	CYP11A1 CYP17 CYP11B1 CYP11B2	4–5	31% at 6 months/ prospective	Increased liver enzymes in 11% cases	Only 1 pivotal trial
Metyrapone	EMA; off-label in US	CYP11B1 CYP11B2	1.9 ± 0.7	43%[a]/retrospective	Increased deoxycorticosterone: hypertension and hypokalemia	Increased androgens; 11 deoxycortisol cross-reactivity with some cortisol immunoassays
Osilodrostat	EMA and FDA	CYP11B1 CYP11B2	3–5	46% at 8 months/ prospective	Increased deoxycorticosterone: hypertension and hypokalemia	Recent approval; only 1 pivotal trial. Same considerations as metyrapone.

[a] 55% had normal cortisol day curves.

Abbreviations: CYP11A1, side-chain cleavage enzyme (desmolase); CYP11B1, 11 beta-hydroxylase; CYP11B2, aldosterone synthase; CYP17, 17 alpha-hydroxylase/17, 20 lyase; CYP21A2, 21-hydroxylase; EMA, European Medical Agency; FDA, US Food and Drug Agency; US, United States.

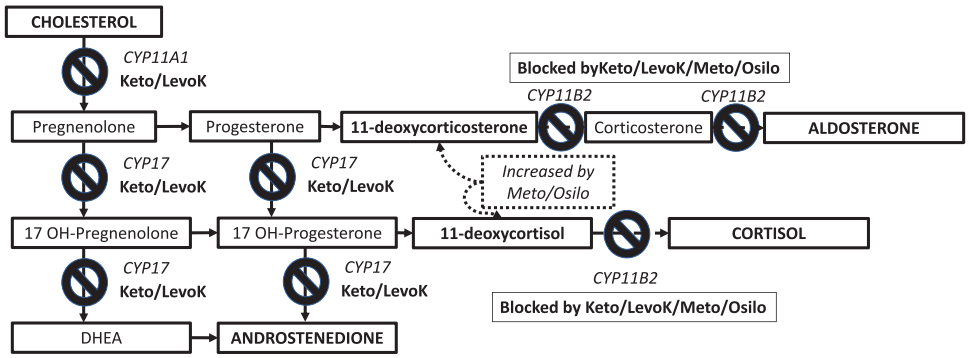

Figure 1. Blockade of steroidogenesis enzymes with ketoconazole (Keto), levoketoconazole (LevoK), metyrapone (Meto), and osilodrostat (Osilo). Metyrapone and osilodrostat can increase the levels of 11-deoxycorticosterone (which might lead to increased blood pressure and hypokalemia), and the levels of 11-deoxycortisol (which might result in false measurements of cortisol). Abbreviatins: CYP11A1, side-chain cleavage enzyme (desmolase); CYP11B1, 11 beta-hydroxylase; CYP11B2, aldosterone synthase; CYP17, 17 alpha-hydroxylase/17, 20 lyase; CYP21A2, 21-hydroxylase; DHEA, dehydroepiandrosterone.

- *Ketoconazole* blocks several enzymes of the adrenal steroidogenesis (Fig. 1), leading to decreased cortisol and (potentially) testosterone concentrations, making its long-term use less preferred in men. Its main side effect is increased liver transaminases in 10%–15% of cases (8,13). Ketoconazole can improve hepatosteatosis by decreasing cortisol levels (14). However, because of the risk of increased liver transaminases, it is usually contraindicated in patients with more than a 3-fold increase in liver enzymes before treatment, and discontinuation is recommended if liver enzymes increase to this level during treatment. Additionally, ketoconazole has many drug-drug interactions mediated by strong inhibition of cytochrome p450 CYP3A4 (15).
- *Levoketoconazole* is the 2S, 4R enantiomer of ketoconazole and blocks the same steroidogenic enzymes. Although preclinical data suggested that liver tolerance might be better than with ketoconazole (16), the proportion of patients with elevated liver enzymes were roughly similar in separate noncomparative studies (10, 13).

- *Metyrapone* is a pyridine derivative that inhibits CYP11B1 and CYP11B2 to reduce aldosterone and cortisol synthesis (Fig. 1). Because of its short half-life, it may be the fastest acting agent, with CYP11B2 blockade achieved by 2 to 4 hours after administration (3). The main short-term side effect is due to the increased levels of the mineralocorticoid deoxycorticosterone, leading to a risk of hypokalemia and hypertension. Hyperandrogenism is a specific long-term side effect, making its chronic use less preferable in women. These side effects can be controlled by adding spironolactone, which blocks the androgen and mineralocorticoid receptors (4).
- *Osilodrostat*, like metyrapone, blocks 11β-hydroxylase and aldosterone synthase. Its longer half-life allows twice daily dosing (3). Short-term side effects of hypokalemia and hypertension are similar to those observed with metyrapone. While hyperandrogenism may appear long-term, the initial report described a transient increase of testosterone after 56 days of osilodrostat, and then a decline to basal values at day 84 of treatment (10).

The goal of treatment with steroidogenesis inhibitors is normalization of cortisol production allowing for improvement, and ideally normalization, in cortisol-induced comorbidities. As detailed in the Endocrine Society guidelines, "monitoring includes assessing clinical response and the biochemical evaluation (24h-UFC, morning serum cortisol, or serum cortisol day curves) to evaluate for hypercortisolism control" (1). We will now focus on the ways to define eucortisolism while monitoring the effects of treatment.

Initiating the Treatment With Steroidogenesis Inhibitors: Choice of Agent, Initial Dose, and Administration Strategy

Choice of agent

Apart from availability and cost, various personal and medical issues influence the choice of a specific steroidogenesis inhibitor:

- Pregnancy and contraception: In general, women with CS are advised not to conceive until hypercortisolism is resolved and comorbidities are controlled, because of the risks of hypercortisolism to both the mother and fetus (17). Thus, women of childbearing age need contraception during treatment with steroidogenesis inhibitors, as eucortisolism might allow for normal ovulation (18). There are only limited safety data on the use of metyrapone during pregnancy (19), and no data on the use of osilodrostat. Ketoconazole (or levoketoconazole) must be avoided in the 1st trimester of pregnancy due to the risk of feminization of the male fetus.
- As mentioned earlier, metyrapone and olisodrostat may exacerbate or induce hypertension, and may have androgenic side effects in women, which may make it a less attractive choice in some patients.
- Ketoconazole requires stomach acidity for optimal absorption and bioavailability, which may be reduced when using proton pump inhibitors (PPIs). Anecdotally, ketoconazole has been used successfully in patients on PPIs, if taken with an acidic beverage such as coke or orange juice. Additionally, many drugs may interact with ketoconazole, which is a strong inhibitor of CYP3A4. Some interactions may be managed by dose adjustment after measuring drug levels, but often this is not available. In vitro data demonstrated that compared to ketoconazole, levoketoconazole had a 2- to 4-fold greater inhibitory action of CYP3A4 (20). Until in vivo human data are available, it seems prudent to regard levoketoconazole as having significant in vivo CYP3A4 inhibition. As mentioned earlier, ketoconazole is not an optimal choice in patients whose liver enzymes are more than 3-fold elevated.
- QT interval: Ketoconazole, levoketoconazole, and osilodrostat can increase the corrected QT interval, thus requiring electrocardiogram (EKG) assessment for safety before initiation (usually performed systematically at diagnosis) and during treatment.
- The potential inability to adhere to a schedule of every 6- to 8-hour administration may shift the choice to osilodrostat or levoketoconazole (or to another class of compounds or treatment option).

Administration strategy and initial dose of steroidogenesis inhibitor

The severity of CS and the benefits of rapid control versus the risk of adrenal insufficiency are considered when choosing the initial dose and administration strategy. The 2 approaches to steroidogenesis inhibitor treatment are "block and replace," generally used in severe or cyclic cases, and a "titration to normalization" approach, most often used in less severe cases. Severe hypercortisolism is characterized clinically by the presence of 1 or more life-threatening comorbidities such as profound hypokalemia, major hyperglycemia, systemic infections and sepsis, venous thromboembolism, peritonitis, or acute psychosis. In such cases, rapid control of hypercortisolism is crucial, requiring high doses of steroidogenesis inhibitors and specific therapies to treat associated comorbidities, including

use of insulin, potassium, antihypertensives, proton pump inhibitors, and antibiotics as appropriate. In these cases, often a block-and-replace strategy is most effective but has not been formally evaluated.

The block-and-replace approach comprises complete inhibition of cortisol production coupled with physiologic glucocorticoid replacement. Corcuff et al illustrated this approach, in which they gave high daily doses of steroidogenesis inhibitor(s) (median starting dose: ketoconazole 900 mg and metyrapone 2125 mg) ((21) refers to the section "When to add a second agent"). "Physiological" doses of hydrocortisone, dexamethasone, or prednisolone are provided to avoid adrenal insufficiency.

This approach has a major advantage in patients with severe CS requiring high doses of steroidogenesis inhibitors and those with cyclical CS. In both scenarios, this approach avoids alternating between hypercortisolism (underdosing) and hypocortisolism (overdosing). However, block and replace regimes are more costly and less convenient due to the need to take more tablets.

In contrast to severely hypercortisolemic patients, rapid control is not as critical in those with a less severe clinical picture, and avoidance of adrenal insufficiency is prioritized. A lower initial dose, with interval progressive dose increases, avoids adrenal insufficiency and can be effective. This titration-to-normalization approach works best in patients with mild-moderate hypercortisolism without large excursions in cortisol production. The steroidogenesis inhibitor is initiated at a low daily doses (eg, ketoconazole 400–600 mg, metyrapone 500–750 mg, osilodrostat 4 mg, levoketoconazole 300 mg) and then progressively increased to reach eucortisolism (see below, "Monitoring").

Dose schedule

Metyrapone and ketoconazole have short plasma half-lives (2–3 hours), which usually necessitates 3 to 4 daily doses, when total daily doses of more than 400 mg of ketoconazole and 500 mg of metyrapone are used. In contrast, due to their longer half-lives, osilodrostat and levoketoconazole can be given twice daily. Interestingly, some experts suggest that the dose schedule and the lowering-cortisol effects should target the circadian rhythm of cortisol, ie, trying to give a progressively higher dose of the drug during the afternoon and evening (with the lowest dose being given in the morning). This approach has been evaluated in a pilot study based on 6 patients with subclinical hypercortisolism: metyrapone given at 6:00 and 10:00 PM to control overnight cortisol hypersecretion decreased the cardiovascular risk marker IL-6 (22).

We Now Return to the Case Above to Place Her Management in the Context of the Issues Described Thus Far

Ms L.A. had moderate hypercortisolism (2-fold increased LNSC and 2-fold increased mean of 2 UFC measurements) and no severe comorbidities. Hypertension was moderate (155/100 mm Hg) without any treatment. Evaluation showed mild hypokalemia (3.3 mmol/l), a normal electrocardiogram (ECG), and a 3-fold increase in liver enzymes. In light of this, a dose titration regime was initiated with metyrapone starting at a dose of 250 mg thrice a day. Spironolactone 25 mg twice a day was given to improve hypertension and hypokalemia. She was educated about potential signs of adrenal insufficiency. A clinical and hormonal evaluation was performed 1 week after treatment initiation. At that visit, hypertension persisted (145/85 mm Hg) and serum potassium was normal. The mean of 2 UFCs was at the upper end of the reference range, but LNSC remained elevated (mean of 2 samples on 2 successive days, 1.5-fold upper limit normal [ULN]). An 8:00 AM serum cortisol was 502 nmol/l (18 ug/dL) after metyrapone intake between 6:00 to 7:00 AM, using an immunoassay without 11-deoxycortisol cross-reactivity. The metyrapone dose was increased, therefore, to 500 mg in the evening, with 250 mg in the morning and at noon. Fifteen days later, the mean of two 24h-UFC was in the midnormal range, LNSCs on 2 successive days were normal, and 8:00 AM serum cortisol was 380 nmol/l (13.8 µg/dl). Serum potassium was 4.2 mmol/l (4.2 mEq/L) and mild hypertension persisted. An additional dose of 25 mg spironolactone was added. Biochemical and clinical monitoring was performed monthly for the next three months, and then every three months.

Monitoring the Antisecretory Efficacy

Endpoints of monitoring

Monitoring of the efficacy of steroidogenesis inhibitors requires assessment of the clinical response, regardless of the dosing strategy, with a goal of normalization of all comorbidities and reversal of Cushingoid features. This is particularly true for clinical stigmata of hypercortisolism, which should improve in the 3 to 12 months following eucortisolism. If not present before hypercortisolism, glucose intolerance and hypertension usually improve quickly. However, hypertension can remain as a sequelae of long-term hypercortisolism, or as a consequence of steroidogenesis inhibitors (increased mineralocorticoid precursors leading to hypertension and hypokalemia in case of 11beta-hydroxylase inhibitors). Assessment should include evaluation of

clinical signs of underdosing (with persistent stigmata of hypercortisolism) or overdosing (with signs suggesting adrenal insufficiency).

Cortisol measurements (urine, saliva, and blood) form the mainstay of monitoring. Thus, clinicians should be familiar with technical issues associated with the assay that is used. These include the type of assay (antibody-based immunoassays or structurally based assays such as liquid chromatography/tandem mass-spectrometry [LC-MS/MS]), the normal range, and patient instructions for the appropriate collection of urine and saliva. Metyrapone and osilodrostat cause significant increases in 11-deoxycortisol, which may cross-react in some (but not all) immunoassays for cortisol. This may potentially lead to inappropriate up-titration of doses, as the measured cortisol may still be high when in reality the true cortisol level is controlled. The risk to the patient is then inducing adrenal insufficiency, unless a block-and-replace regimen is used. It is important to determine cross-reactivity of 11-deoxycortisol if an immunoassay is used for monitoring. If the cross-reactivity is high, an LC-MS/MS assay for cortisol should be used, or a different agent should be chosen.

Hormonal monitoring in patients undergoing dose titration without blockade

- 24h-UFC theoretically represents the best way to determine the integrated daily amount of cortisol production and has been the main marker of antisecretory efficacy used in most studies of steroidogenesis inhibitors (7–10). Petersenn et al demonstrated wide variability of 24h-UFC in patients treated with pasireotide, and it is likely that the same variability would apply to steroidogenesis inhibitors (23). In that report, the intrapatient coefficient of variation for mean UFC (mUFC) was 38% for 2 samples and rose to 51% when evaluating 4 samples. Based on this amount of variability, an absolute UFC change of less than 50% could be due to a random effect rather than drug efficacy. Interestingly, the highest variability was observed in patients with highest mUFC. Reaching normal UFC thus seems mandatory to exclude severe hypercortisolism, but does not exclude mild hypercortisolism or hypocortisolism.
- Late night (bedtime) salivary cortisol has the main advantage of evaluating the nadir of cortisol, a measure that is difficult to obtain routinely using serum. However, steroidogenesis inhibitors given in equal doses during the day tend to reduce serum cortisol levels equally at any time of the day. Because patients with CS lose the bedtime cortisol nadir and may have similar cortisol levels at all times of the day, only patients with mild hypercortisolism would be expected to have a normal LNSC, and efforts to normalize the value when using equal doses of these agents are likely to result in hypocortisolism. This theoretical consideration was shown to be true in the phase 3 study of pasireotide long acting release (LAR), in which the mean LNSC of 2 samples was evaluated in 137 patients measured the 1st 2 days of 3 UFC collections. After 7 months, 56 patients had controlled mean UFC, and 25 had controlled mean LSNC, while only 20 had both controlled mean UFC and mean LNSC. Importantly, 36 patients had increased mean LSNC despite normal mean UFC, while 5 had had increased mean UFC despite normal mean LSNC. Similar results were found at month 12, showing that these 2 parameters were only mildly correlated (24, 25). The optimal metabolic profiles were observed in patients with both normal mean UFC and LNSC (26). These data suggest that normalization of LNSC is important for clinical recovery and demonstrate that research is needed to establish whether higher evening doses of steroidogenesis inhibitors would facilitate clinical recovery by normalization of LNSC.
- Morning cortisol values should be evaluated regularly, even in patients considered controlled and on a stable dose of steroidogenesis inhibitors. This may be especially pertinent in patients having higher evening doses (than the one given in the morning) in a "reverse circadian" fashion, and/or in patients who reached a low-normal LSNC. Low cortisol on therapy could be defined by 2 measurements of 8:00 AM cortisol between 80 and 140 nmol/l (3–5 µg/dl). While morning serum cortisol is important to rule out adrenal insufficiency, some authors proposed to evaluate the efficacy of drugs by measuring 3 to 8 serum cortisol samples throughout the day, as mentioned in the Endocrine Society guidelines (1), with a target of a mean serum cortisol level between 150 and 300 nmol/L (5.5–11 µg/dl) (27). For instance, this has been used to define the antisecretory efficacy of metyrapone (7): in that study, at last follow-up, 50% of patients were considered controlled based on serum cortisol "day curves," versus 35% based on 24h-UFC. These serum cortisol day curves could be useful especially when LSNC is not available, but are more cumbersome. Measurement of serum cortisol cannot be relied upon in states when cortisol binding globulin (CBG) is elevated, such as in pregnancy or patients on exogenous estrogens; in these situations UFC should be used using a pregnancy-based reference range as appropriate. A simpler alternative to a day curve is to use a single early morning cortisol value,

with a target of 8 to 10 ug/dl, which approximates the mean cortisol value in a healthy person over 24 hours, with an assumption that the patient lacks cortisol diurnal variation. A morning cortisol level can be compared to the UFC, and if it correlates well, can substitute for UFC measurements if the patient is otherwise improving.

Monitoring in a block-and-replace approach

It is difficult to predict the dose of steroidogenesis inhibitor needed to completely block cortisol production, since UFC values are quite variable, particularly in some patients with severe hypercortisolism. As a result, it is important to ensure that multiple morning cortisol levels and/or UFC are completely inhibited (ie, are extremely low). If serum cortisol values are used, the time from the last treatment dose must be taken into account, and ideally a trough (predose) value is obtained to ensure that there is no rebound from the earlier dose.

Once suppression is achieved, a 2nd difficulty is to determine the optimal dose of substitutive treatment to avoid mild hyper- or hypocortisolism. For hydrocortisone, the classical dose is identical to the one used in primary adrenal insufficiency (20 mg/day). Few studies have tried to optimize the dose of hydrocortisone in adrenal insufficiency. Mah et al defined an optimal dose based on weight (0.12 mg/kg), and measurements of serum cortisol 4 hours after hydrocortisone intake (target to reach: 90–230 nmol/l to 3.2–8.4 µg/dl) (28). Rousseau et al used a theoretical dose based on body surface, with a dose schedule of 2/3 in the morning and 1/3 at noon: serum targets to reach were < 400 nmol/l (14.5 µg/dl) 2 hours after morning intake, and < 250 nmol/l (9 µg/dl) 4 hours after noon intake (29). Others use body surface area related to cortisol production, of 10 to 12 mg/m^2 daily. No study has examined whether comorbidities and quality of life were improved based on these doses. Even though these 4 steroidogenesis inhibitors also block the CYP11B2 (aldosterone synthase), an additional dose of fludrocortisone is rarely necessary except in patients with low blood pressure.

Frequency of hormonal monitoring

Like many other decisions related to these medications, the frequency of monitoring is tailored to the severity of hypercortisolism. Patients with mild (UFC less than 2-fold elevated) or moderate disease (UFC 2- to 5-fold elevated) might be checked initially 1 to 2 weeks after drug initiation. If UFC was normalized, and pretreatment UFC values were relatively consistent, a subsequent check 2 to 3 weeks later should validate continued efficacy. When a dose adjustment is made (either an increase or decrease), the clock "resets" so that the next check occurs 1 to 2 weeks later, and so on until normalization occurs.

Patients with severe hypercortisolism may be started on medical treatment as an outpatient or as an inpatient. Outpatients may be checked every week until the goal is met consistently. Inpatients who have very severe disease may require daily serum cortisol checks to predict whether they need an increased dose within 3 to 5 days. Ideally, such patients should be treated in a center with significant experience in assessing these patients, who may have life-threatening complications.

Monitoring for the specific side effects of steroidogenesis inhibitors

Patients with anorexia, nausea, or diarrhea should be evaluated for adrenal insufficiency. If excluded, they can try taking their medications with a meal or snack, although no study has evaluated the utility of this strategy. We will focus on 4 specific side effects:

- Adrenal insufficiency can occur with any of these agents. Patients should be thoroughly informed about the associated clinical signs (nausea, anorexia, intense fatigue, low blood pressure with dizziness on standing) and about emergency management, including when to stop the drug(s), initiating glucocorticoid replacement at home or in the emergency department, and informing their endocrinologist. Ideal practice would be to provide a parenteral hydrocortisone pack for emergency injection via the subcutaneous or intra-muscular route, and to educate patients in its use and limitations, emphasizing that if the injection is needed the patient still needs to seek medical professional advice and may need to attend the emergency room. Patients need to be warned that adrenal insufficiency can happen any time after the treatment initiation, even after a prolonged period of time, and even on a constant dose.
- Elevated liver enzymes on ketoconazole and levoketoconazole. In the largest retrospective study on ketoconazole for CD, liver enzymes increased to 5-fold above the reference range in 15.8% of patients (30/190), up to 5- to 10-fold in 4 patients and more than 10-fold in 1. Liver enzymes normalized 2 to 4 weeks after dose decrease or discontinuation. No significant increase was reported after the 1st month of initiation or after a dose increase (8). An analysis of the compassionate use programme of ketoconazole in France reported a similar temporal pattern, but fewer liver enzyme abnormalities (less than 10%) (13). In the SONICS phase 3 trial of levoketoconazole, 10 patients

(11%) presented with an alanine aminotransferase (ALT) more than 3 times the ULN, which was fully reversible (10). Based on these data, we suggest that liver enzymes be measured weekly during the 1st month and after each dose increase.

- Hypokalemia and hypertension on 11 beta hydroxylase blockers. In the retrospective metyrapone study, potassium, spironolactone, and antihypertensive drug use was noted but not further described. Potassium levels were monitored and hypokalemia was treated during treatment without recurrence; the final potassium level was significantly higher than the pretreatment value. Hypertension did not worsen (7). In the LINC3 phase 3 study on osilodrostat, hypokalemia was reported in 7/137 patients (5.1%) requiring potassium supplementation, spironolactone, and/or dose decrease; osilodrostat was discontinued due to worsening of high blood pressure in 1 patient (9). Hypokalemia and/or hypertension should thus be treated with potassium and/or spironolactone to prevent further deterioration during CYP11B2 inhibitor treatment.
- Hyper- and hypoandrogenism may occur with long-term use of CYP11B2 inhibitors or levo/ketoconazole, respectively. In the retrospective metyrapone study, hyperandrogenism was infrequent, hirsutism was not reported and only 1 patient complained about worsening acne (7). In the LINC-3 phase 3 trial on osilodrostat, women had a 2-fold increase of testosterone levels from baseline to week 48 (mean testosterone concentrations 1.3 nmol/L vs 2.6 nmol/L) (0.4–0.8 µg/L) (9). Of note, while ketoconazole might lead to hypoandrogenism on a long-term basis, this has never been clearly demonstrated, perhaps because hypogonadism is common in hypercortisolemic men. In the maintenance phase following the SONICS trial of levoketoconazole, there was no significant change in testosterone in men, while it was decreased in women after 6 months of treatment versus baseline (30).

When to Add a Second Agent

Adding a second steroidogenesis inhibitor is useful in 2 situations:

- When 1 drug does not control hypercortisolism.

In the study by Daniel et al, 29 patients were treated with metyrapone and ketoconazole or mitotane, including 22 in whom the 2nd drug was added to metyrapone monotherapy because of partial efficacy or adverse effects. The antisecretory efficacy was not different between patients on monotherapy or combination therapy. The final median metyrapone dose in patients controlled with combination therapy was 1500 mg per day (7). Two studies evaluated the ketoconazole and metyrapone combination in patients with severe hypercortisolism (median UFC 30- to 40-fold ULN), especially in ectopic ACTH secretion. In the Corcuff study, combination therapy was highly effective in controlling hypercortisolism (73% of 14 patients with ectopic ACTH secretion, and 86% of 8 patients with adrenocortical carcinoma), with initial doses of ketoconazole from 400 to 1200 mg/day, and metyrapone from 500 to 4500 mg/day (21). The other retrospective study used an initial median dose of 2250 mg/24 hour metyrapone and 800 mg/24 hour ketoconazole, with ranges of dose comparable to the Corcuff study, in addition to mitotane 3 to 5 g/d (31). Both studies found a major decrease in 24h-UFC by day 7. In patients with severe hypercortisolism, high doses should be used at initiation to try to rapidly control hypercortisolism.

There is only 1 report of the addition of pituitary targeted drugs to steroidogenesis inhibitors in patients with CD. That prospective study evaluated the addition of ketoconazole (200 mg thrice daily) to combination pasireotide and cabergoline if hypercortisolism was not controlled. By the end of the study, 88% of the 17 patients had normal 24h-UFC (32). Future research is needed to evaluate the benefits and side effects of such an approach.

When a dose-dependent side effect is observed

Here, the dose of steroidogenesis inhibitor could be decreased, and a complementary dose of another steroidogenesis inhibitor with another mechanism could be added at a low dose. For instance, ketoconazole or levoketoconazole dose could be decreased, and a small dose of metyrapone added in patients with worrisome liver enzyme increases on ketoconazole. Similarly, in women with hyperandrogenism induced by metyrapone or osilodrostat, the dose could be decreased and a small dose of ketoconazole or levoketoconazole added.

When a second agent is added, monitoring should follow the same guidelines as those used initially for monotherapy, taking into account the need for additional evaluation of liver function as well as the usual monitoring of secretory efficacy.

Additional Treatment Considerations

In addition to the use of steroidogenesis inhibitors, all comorbidities should be treated specifically and usual preventive care should continue. For example, we suggest that all adult patients receive age-appropriate routinely recommended recombinant or inactivated vaccines, avoiding live attenuated vaccines (33). Influenza

prophylaxis is important, since CS patients are especially vulnerable to this disorder. In 2021, we recommend that providers consider vaccination for the prevention of Coronavirus Disease 2019 (COVID-19), according to country-specific recommendations. Use of steroidogenesis inhibitors during high SARS-CoV-2 prevalence has been discussed elsewhere (33).

Finally, each drug can have a variable cost depending on the country, and this should be taken into account in patients for whom a long-term treatment might be needed.

Conclusions

Monitoring the efficacy and side effects of steroidogenesis inhibitors is a challenging task. Combining biological markers is probably the best option to ensure eucortisolism, even if each marker per se has its own limits (especially a high degree of variability for LNSC and UFC, requiring repeated measurements). Due to the risk of a complete blockade of adrenal steroidogenesis, it is imperative to educate patients, their family, and caregivers about the signs of adrenal insufficiency and how to address these. As no study has demonstrated complete normalization of clinical signs and symptoms, additional research is needed to optimize this approach to the treatment of hypercortisolism.

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