MEDICAL TREATMENTS IN CUSHING'S SYNDROME: NEW INSIGHTS

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Altogether to Beat
Cushing's Syndrome

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ALTOGETHER TO BEAT CUSHING'S SYNDROME

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NOVITÀ IN TEMA DI TERAPIA MEDICA
DELLA SINDROME DI CUSHING

MEDICAL TREATMENTS IN CUSHING'S SYNDROME:
NEW INSIGHTS

Introduction

Cushing's syndrome (CS) is a serious clinical condition caused by endogenous or exogenous cortisol excess, known as hypercortisolism.

Endogenous CS is a rare endocrine disorder caused by chronic excessive cortisol secretion from the adrenal glands, with an estimated prevalence of 40 cases per million people and incidence of 0.7–2.4 cases per million people per year. Endogenous CS has a higher prevalence in females and is more frequent during the fourth to sixth decades of life, although occurring at any age.

In approximately 80% of cases, endogenous CS is a consequence of an adrenocorticotropin (ACTH) hypersecretion (ACTH-dependent CS), generally due to a ACTH-secreting pituitary tumor (Cushing's disease, CD, 70%), and, rarely, to an ACTH-secreting or corticotrophin releasing hormone (CRH)-secreting extra-pituitary tumor (Ectopic CS, ECS, 10%). In the remaining 20% of cases, CS is a direct consequence of autonomous cortisol overproduction by the adrenal glands (ACTH-independent CS), because of unilateral or bilateral adrenal diseases.

Clinical picture of CS has a variable expression resulting from a constellation of different signs, including weight gain, moon face, facial plethora, buffalo hump, supraclavicular and dorsal fat pads, purple striae, diffuse bruising, skin thinning, proximal myopathy, hirsutism, acne and alopecia, as well as symptoms, mainly including asthenia, fatigue, and mood disorders.

The clinical picture is complicated by several comorbidities, including metabolic syndrome, characterized by visceral obesity, systemic arterial hypertension, impairment of glucose metabolism and dyslipidaemia, strictly associated with cardiovascular diseases, including vascular atherosclerosis and cardiac damage, which, together with thromboembolism and hypokalaemia, contribute to the increase in cardiovascular risk. Additional clinical complications include musculoskeletal diseases, such as myopathy, osteoporosis and skeletal fractures; neuropsychiatric diseases, such as impairment of cognitive function, mania or depression; immune disorders with higher susceptibility to infections, possibly complicated by sepsis; impairment of reproductive and sexual function with consequent infertility or sexual disturbances. The constellation of all these comorbidities is associated with an increased morbidity and mortality, mainly for cardiovascular diseases and sepsis, and with an impaired quality of life (QoL).

Therefore, a prompt screening, a confirmatory diagnosis, and an effective multidisciplinary therapeutic approach are mandatory in the attempt to improve clinical picture, morbidity, QoL, and mortality.

CS is a clinical challenge during both diagnosis and treatment, and its burden may persist

long ever after disease control or remission, requiring therefore a careful follow-up over time.

Treatment goals should include the normalization of cortisol levels, the reversion of clinical signs and symptoms, the prevention or improvement of the concomitant comorbidities, the control of tumor growth, the long-term control without recurrence, and the restoration of normal mortality ratio.

The main treatment approaches include surgery, radiotherapy, and medical treatment. Surgery represents the first line treatment for all CS forms. Second line treatment approaches are strictly dependent on CS etiology. CD approaches include repeat pituitary surgery, pituitary radiotherapy, bilateral adrenalectomy, and medical treatment. ECS approaches mainly include radiotherapy or chemotherapy, bilateral adrenalectomy, and medical treatment. Lastly, adrenal CS approaches include chemotherapy, radiotherapy, and medical treatment. A multimodal and individualized approach is suggested considering the high rates of CS persistence and recurrence, especially for CD and Ectopic CS.

Medical treatment

Medical treatment has historically played a minor role in the CS management; however, recently, thanks to the availability of novel compounds and to the employment of drugs previously used with different indications, it has been acquiring a more important role in different steps of the treatment schedule.

Particularly, in case of CD, medical treatment can be advocated before pituitary surgery, as preoperative treatment, especially in patients with severe disease, in order to control cortisol excess and improve the clinical picture, or after pituitary surgery, as adjuvant treatment, in patients with persistent or recurrent CD, before or after pituitary radiotherapy, or, lastly, as primary alternative treatment in case of contraindication to surgery, for instance, in patients with invisible tumors or with tumors with unfavorable location or extra-sellar expansion, or in case of refusal of surgery.

The spectrum of available drugs includes three main categories of compounds: (1) the pituitary-directed agents, which act at the pituitary level by inhibiting ACTH, and, only secondarily, cortisol secretion; (2) the adrenal blocking agents or steroidogenesis inhibitors, which act at the adrenal level by blocking cortisol production, by inhibiting steroid hormone synthesis; (3) the glucocorticoid receptor (GR) antagonists, which block the activation of GC receptors.

Pituitary-directed drugs include **pasireotide**, approved medical treatment for CD not willing or unable to perform neurosurgery, an effective therapy able to control both hormonal and clinical burdens and to induce tumor shrinkage in selected cases, although a careful monitoring of glucose metabolism should be performed in all treated patients, and **cabergoline**, that has shown promising results in patients with mild CD with a good safety profile.

Adrenal-directed drugs are highly effective in CS control and mainly include adrenal steroidogenesis inhibitors **ketoconazole**, that may be associated with hepatic enzymes alteration, QT prolongation, and male hypogonadism, and **metyrapone**, that may induce hypokalemia and hirsutism in females. New generation steroidogenesis inhibitors, including **levoketoconazole** and **osilodrostat**, are under investigation in phase III studies; they are hypothesized to provide better efficacy and safety, compared with conventional steroidogenesis inhibitors.

GR antagonist mifepristone is effective in inducing remission of CS clinical features but monitoring of its efficacy is challenging due to the absence of reliable biomarkers. The new GR antagonist **Relacorilant** represents an interesting and innovative potential compound for CS treatment, under investigation in phase II studies.

Pituitary-directed drugs

PASIREOTIDE AND CABERGOLINE

Pasireotide, a new multiligand somatostatin analogue with high affinity for somatostatin receptor type 5 (SSTR5), which is highly expressed in ACTH-secreting pituitary tumors, is the first medical therapy officially approved for the treatment of adult CD patients, which experienced a failure of pituitary surgery, or are not candidates for pituitary surgery and require medical therapeutic intervention. Pasireotide, subcutaneously administered twice daily, at a dosage of 300–900 μg, has shown remission rates, in terms of cortisol excess control, ranging from 17% to 22.2% in the short-term follow-up (shorter or equal 12 months), reaching 34.5% (longer 24 months), 68.8% (up to 5 years), and 50% (up to 10 years) of cases in the long-term follow-up. Notably, cortisol reduction appeared to be accompanied by an improvement in clinical picture and metabolic profile, including facial rubor, bruising, supraclavicular and dorsal fat pads, weight, body mass index, waist circumference, blood pressure, and total and LDL-cholesterol levels, as well as depression and QoL. Moreover, pasireotide has also been demonstrated to be able to reduce pituitary tumor volume in 46.3–100% (m = 73.15%) of patients at 12- months follow-up. As far as safety profile was concerned, pasireotide is generally well tolerated: the most frequently reported significant adverse events were hyperglycemia-related events (72.8%), diarrhea (58%), nausea (52%), cholelithiasis-related events (30%), mild transient elevations in liver enzyme levels (29%), headache (28%), abdominal pain (24%), fatigue (19%), asthenia (11%), hypocortisolism-related events (8%), and prolongation of the corrected QTc interval >480 msec (2%). Compared with conventional somatostatin analogues, pasireotide is associated with a higher rate of hyperglycemia-related adverse events, due to the decrease in insulin and incretin secretion. During treatment, patients need to be carefully monitored, and an appropriate antidiabetic therapy should be initiated with metformin and staged treatment intensification with a dipeptidyl peptidase-4 inhibitor, with a switch to a GLP-1 receptor agonist and initiation of insulin, as required, to achieve and maintain glycemic control.

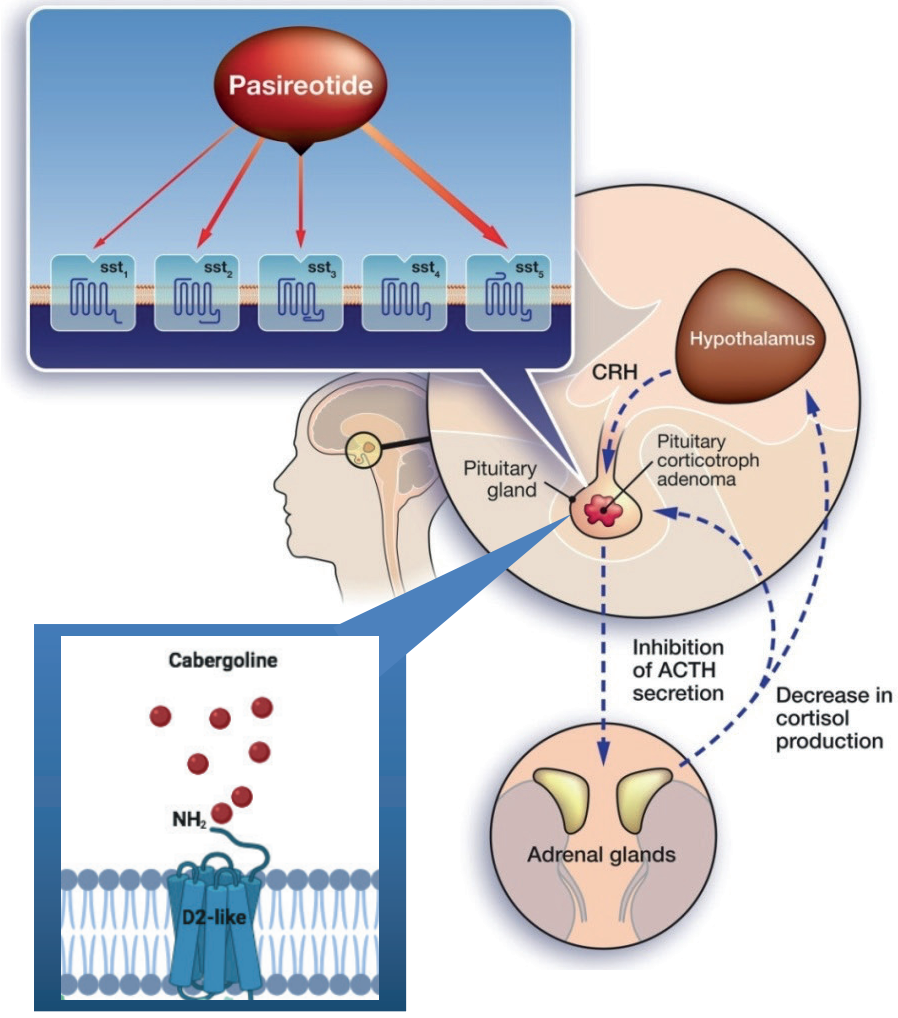
Pasireotide long acting release (LAR), a new formulation with monthly administration at a dosage of 10–30 mg, is shown to be more efficacious, compared with the subcutaneous formulation, being effective in approximately 40% of CD patients, improving clinical signs and symptoms, and Cushing QoL score; most commonly reported adverse events were hyperglycaemia-related occurring in 76.7% of patients.

Cabergoline, a powerful agonist of dopamine receptor type 2 (D2), which are highly expressed in ACTH-secreting pituitary tumors, is currently an off-label treatment for CD. Cabergoline, orally administered at dosages of 0.5–7 mg/week, has shown remission rates, in terms of cortisol excess control, of 25–40% (m = 31.2%), associated with an improvement in the clinical picture, mainly hypertension and glucose intolerance, with an escape rate of

18.2–33.3% (m = 25%) in patients with a documented initial response. Moreover, in 50% of patients, tumor shrinkage has been described. As far as safety profile was concerned, cabergoline is very well tolerated with rare adverse events reported, including hypotension and severe asthenia (10–20%, m = 15%), dizziness and nausea (5–25%, m = 13.3%). The increased risk of cardiac valve diseases, which has been reported at the higher doses used for neurological disorders, is less important at the lower dosage used to treat CD. Nevertheless, further controlled studies on larger populations of patients are needed to evaluate the clinical advantages, in terms of drug benefits and side effects.

Addition of cabergoline to pasireotide monotherapy in patients with persistent hypercortisolism may be an effective strategy to enhance the CD control.

Pasireotide and Cabergoline

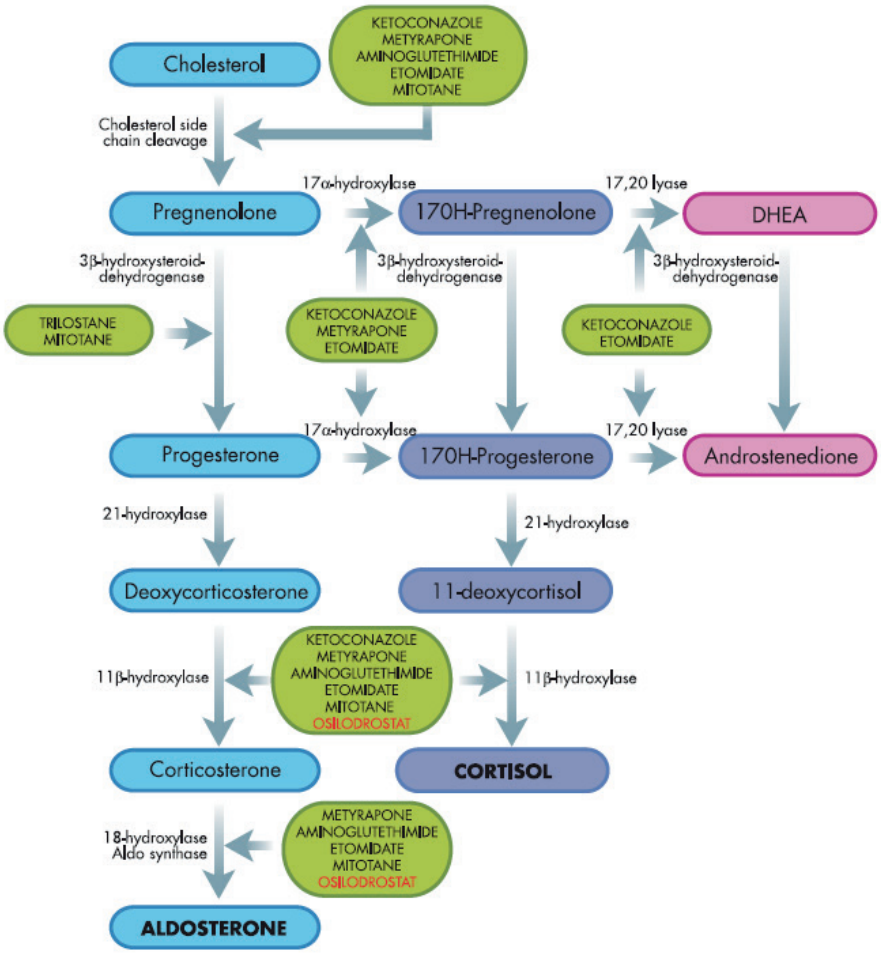


Adrenal-directed drugs: Steroidogenesis inhibitors

KETOCONAZOLE

Ketoconazole, an imidazolic antifungal agent constituted of a 50/50 racemic mixture of 2S,4R and 2R,4S entiomers, acts by blocking different adrenal steroidogenesis enzymes (cholesterol side-chain cleavage complex, 17α-hydroxylase, 17,20-lyase, 11β-hydroxylase), and consequently reducing cortisol synthesis.

It has been used most widely "off-label" for the treatment of hypercortisolism and, in November 2014, it has been officially approved by EMA for the treatment of patients older than 12 years, suffering from CS. Apart from adrenal blocking effects, ketoconazole may also have direct effects on corticotroph tumor cells in patients with CD. Surprisingly, evidences on mouse and human ACTH-secreting pituitary tumor cell lines have demonstrated its efficacy in inhibiting ACTH secretion and cell growth by the induction of apoptosis.



In clinical practice, ketoconazole is administered at dosages ranging from 200 to 1200 mg/day, with an effective dose of 600-800 mg/day in the majority of cases. It has a rapid absorption, but its relatively short half-life (1-3 h) requires a twice/thrice daily dosing during treatment. Ketoconazole has a quick onset of action and has been demonstrated to be effective in normalizing cortisol levels in about 44.7% to 92.9% of patients (m =65%), with escape rates of 7.1–22.7% (m = 14.5%) registered in initially responsive patients. It should be considered that these remission rates are extrapolated by studies analyzing patients suffering from all CS forms, including CD but also adrenal CS and ECS, resulting in overall CS remission rates of 84.6–94.1% (m = 89.3%). Notably, cortisol reduction appeared accompanied by an improvement in signs and comorbidities of CD, including body weight, hirsutism, myopathy and muscle weakness, bone status, psychiatric symptoms, glucose metabolism, and blood pressure.

One of the problems with ketoconazole is the paucity of published data and the lack of prospective studies concerning its use in the context of CS. Nevertheless, a recent retrospective study including 200 patients from 14 different French centres has demonstrated that ketoconazole is a highly effective drug lowering circulating cortisol levels, even in the long-term, with an acceptable tolerability profile, since hepatotoxicity, the most significant issue with ketoconazole treatment, was a relatively frequent event but remained moderate in most of the patients. Overall, the benefit/risk balance should remain in favour of ketoconazole use in patients requiring medical treatment for CS. Ketoconazole has been used in a number of pregnant women with good maternal and fetal outcomes. It has also been used successfully in children and in the elderly, but conclusions on its safety in these populations require studies on a larger number of patients.

As far as safety profile was concerned, Ketoconazole is a well-tolerated medication, although attention needs to be paid to liver function. Indeed the most severe and frequent adverse event related to ketoconazole is hepatotoxicity, occurring in 2.6–18.7% of cases, early after starting treatment or at dosage increase, requiring a strict monitoring of liver enzymes and bilirubin levels, particularly within the first month of treatment. Fatal hepatitis is rarely reported in patients using ketoconazole as antifungal drug. Additional adverse events, less frequently reported, include gastrointestinal disturbances, skin rash, adrenal insufficiency, pruritus, fatigue, headache, and gynecomastia. Considering the impact of ketoconazole on gonadal testosterone synthesis, which results in hypogonadism, this drug should be preferred in females.

LEVOKETOCONAZOLE

Levoketoconazole (COR-003) is the cis-2S,4R enantiomer of ketoconazole and is currently under evaluation in prospective clinical trials for CS treatment. Levoketoconazole is a new adrenal blocker that inhibits the steroidogenesis enzymes CYP17, CYP11β1 and CYP21 more potently than ketoconazole, potentially allowing lower drug doses. Preclinical data suggest that levoketoconazole suppress corticosterone in rats more potently than ketoconazole or placebo.

In healthy subjects after 4 days of treatment, a significant decrease in serum cortisol was seen with levoketoconazole as compared with placebo and racemic ketoconazole. Always in phase I studies, after 5 days of dosing with racemic ketoconazole, maximal plasma concentration of levoketoconazole was about 3-fold higher compared with the 2R,4S enantiomer and it was generally well tolerated.

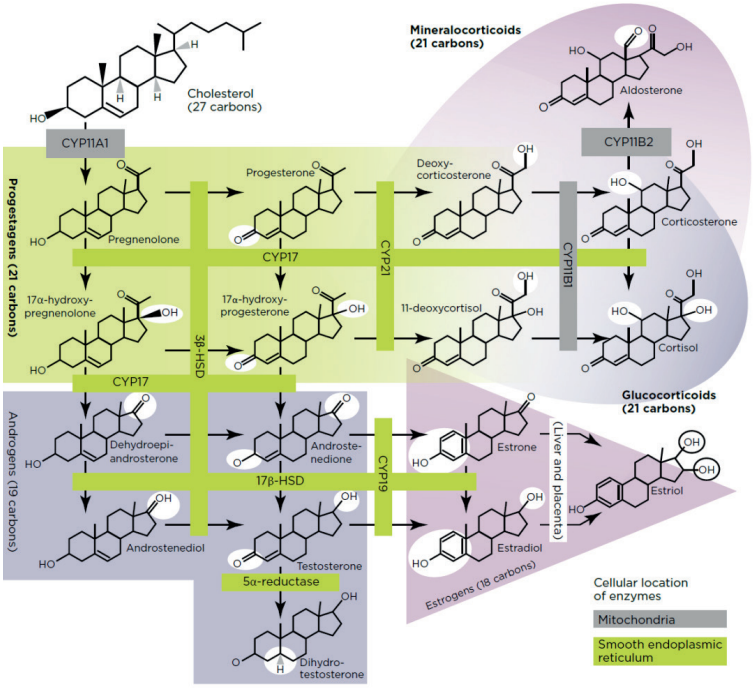
The results of a phase III, multicentre, open-label, single-arm trial (SONICS), evaluating the efficacy and safety of levoketoconazole in the treatment of endogenous CS, has been recently published. Between July 30 2014 and June 30 2017, 201 individuals were screened and 94 patients (80 CD patients; 85%) were enrolled and received at least one dose of study medication in 60 different centres (19 countries). Patients were treated with oral levoketoconazole in

a 2–21-week dose-titration phase until 24-h urinary free cortisol (mUFC) normalization (300-1200 mg in two doses per day) and a 6-month maintenance phase. The primary outcome was the complete response rate, defined as the proportion of patients with mUFC at or below the upper limit of normal (ULN) at the end of the maintenance phase, without an increase in dose at any time during maintenance. This primary outcome was achieved, indeed at the end of the maintenance phase, 29 (31%) of 94 (intention-to-treat population) patients were responders allowing to reject the null hypothesis (proportion of responders at the end of the maintenance phase equal or lower than 20%). The rate of response was even higher (34 patients had normalized mUFC; 62%) when the 55 patients who completed the maintenance phase with both baseline and end of the maintenance phase data were considered as study population. Mean late-night salivary cortisol decreased from baseline to month 6 of maintenance; however, only 4 patients had normal late-night salivary cortisol levels at end. Mean ACTH increases, but there was no correlation between changes in ACTH and change in mUFC. Significant mean improvements from baseline at end of the maintenance phase were observed in several of the CS comorbidity biomarkers: fasting blood glucose concentration, HbA1c, total and LDL cholesterol, and body weight. Significant mean improvements in clinician-rated acne, hirsutism (among females), and peripheral edema scores were noted. Patient reported outcomes of QoL and depression severity significantly improved from baseline to month 6.

Most adverse events were of mild or moderate intensity (grade 1–2). The most common adverse events were nausea (32%) and headache (26%). Adverse events led to study discontinuation in 12 (13%) of 94 patients. Two patients had a QT interval prolongation, and three patients had suspected adrenal insufficiency. Alanine aminotransferase reversibly increased to more than three times the ULN in ten (11%) patients. Four patients had serious adverse events that were considered probably or definitely related to the study drug: abnormal liver function test results (n=1), prolonged QT interval (n=2), and adrenal insufficiency (n=1). One patient died from colon carcinoma unrelated to study medication.

The strengths of this study are: it represents the first prospective clinical trial with a ketoconazole-derived drug in CS; it used an intention to treat analysis; no upper limit of mUFC was considered as inclusion criteria; it reported beneficial outcomes on clinical parameters. The

Levoketoconazole



Enzyme	IC_{50} (nM)[2]	
	Racemic Ketoconazole	Levo-Ketoconazole
CYP17	93	48
CYP11β1	840	116
CYP21	2450	1000

CYP, cytochrome P450; HSD, hydroxysteroid dehydrogenase.

limitations of this study are: the absence of a direct comparison with ketoconazole, the open label, non-controlled study design.

A double-blind, placebo-controlled, randomized withdrawal following open-label therapy study to assess the safety and efficacy of Levoketoconazole (2S, 4R-ketoconazole) in the treatment of endogenous CS (LOGICS) is currently ongoing.

Levoketoconazole may be effective at lower doses providing a healthier safety profile compared to ketoconazole, but further studies are still required to fully understand its role in the medical management of CS.

METYRAPONE

Metyrapone, a pyridine derivative, acts by blocking different adrenal steroidogenesis enzymes (cholesterol side chain cleavage, 17α-hydroxylase, 18-hydroxylase and particularly 11β-hydroxylase complex), and consequently reducing cortisol synthesis. Particularly, it inhibits the final step in cortisol synthesis, namely the conversion of 11-deoxycortisol into cortisol by 11β-hydroxylase (CYP11B1), achieving a nadir in cortisol levels within 2 hours of its administration.

Metyrapone has been successfully used in some countries for 40 years. The compound is officially approved for treatment of patients suffering from CS. Orally administered at a dosage of 500–6000 mg, four or six times daily, it has shown remission rates, in terms of cortisol excess control, ranging from 45.4% to 100% (m=71%), with escape rates of 0–18.7% (m=7.8%) registered in initially responsive patients. However, it should be considered that, also for metyrapone, the mentioned remission rates are extrapolated by studies analyzing patients suffering from all CS forms, resulting in overall CS remission rates of 56.5–80% (m = 70.8%). A recent observational prospective study has shown that metyrapone has a rapid-onset, a long-term effectiveness and is a safe medical treatment in CS patients, achieving UFC normalization (in 70% of patients) more than salivary cortisol rhythm recovery (in 37% of subjects). Notably, measuring cortisol could be an issue during metyrapone treatment: the increase in steroid precursors can result in cross-reaction, especially using immunoassay. Therefore, spectrometry methods are suggested by guidelines, and should be used in routine clinical practice when available. Cortisol reduction appeared accompanied by a rapid improvement in signs and symptoms of CD, including facial plethora, round face, muscle weakness, psychiatric symptoms, glucose metabolism, and blood pressure.

Metyrapone has been the most commonly used medical therapy in pregnant women with CS. The relationship between metyrapone administration and the incidence of pre-eclampsia, strictly related to the persistence or worsening of hypertension, has been largely debated. However, the coadministration of metyrapone with an antihypertensive drug is recommended to guarantee a safer outcome during pregnancy.

As far as safety profile was concerned, metyrapone is well tolerated, and the most frequent adverse events are hyperandrogenism in females, reported in 4.5–71.4%, hypertension in 48.4%, and hypokalemia in 6.7–13.6% of patients. These adverse events are due to ACTH increase, with consequent androgen and cortisol or aldosterone precursors overproduction. Therefore, adverse events related to elevated mineralocorticoids (low-renin hypertension, edema and hypokalemia) and androgens (acne and hirsutism in females) have to be considered before starting metyrapone. Considering the impact on androgen synthesis, this drug should be preferred in males. Additional less frequently reported adverse events include dizziness, headache, arthralgia, myalgia, fatigue, gastrointestinal disturbances, adrenal insufficiency, and skin rash. Metyrapone can be considered an effective drug in the medical management of CD; it is mainly advised for short-term treatment but is occasionally used for chronic treatment.

OSILODROSTAT

Osilodrostat (LCI699), is a new adrenal directed drug, which exerts a potent inhibition of 11 β-hydroxylase (CYP11B1), the enzyme that catalyses the final step of cortisol synthesis, by consequently reducing cortisol synthesis, representing a novel and potential new treatment for CD, and theoretically for all forms of CS. It has a half-life of □4 hours that allows twice-daily oral administration. LCI699 also inhibit aldosterone synthase (CYP11B2), reducing significantly the aldosterone levels.

In a 10 week proof of concept study, osilodrostat demonstrated good efficacy in normalizing UFC in 92% of patients with CD with a good safety profile. UFC returned to baseline levels when the treatment was stopped.

The extension phase II study (LINC2) enrolled 19 patients with CD with UFC more than 1.5 x ULN. The initial dose was 4 or 10 mg daily depending on the degree of UFC values. Doses were increased every two weeks until UFC normalization and to a maximal dose of 60 mg/day. At 22 weeks, overall response rate, represented by patients with UFC normalization and patients with a ≥ 50% UFC reduction, was 89.5% (17/19 patients). UFC normalized in 78.9% (15/19) of patients. UFC levels decreased rapidly by week 4 and remained suppressed through the study. Morning plasma and salivary cortisol also decreased to normal levels, meanwhile the response of late-night salivary cortisol was variable maintaining high levels throughout the study. ACTH levels increased during treatment, as a possible compensatory reaction to the reduction in cortisol levels. This led to expected increases above normal in 11-deoxycortisol and 11-deoxycorticosterone.

Notably, cortisol reduction appeared accompanied by a modest improvement in glucose and lipid profile. Mean body weight and blood pressure levels were relatively unchanged during the study. A possible effect of the mineralocorticoid precursors on these parameters cannot be excluded. Minimal changes in pituitary imaging were seen in this study, but longer follow-up is needed to explore this item more carefully.

Osilodrostat treatment was generally well tolerated showing as most common adverse events asthenia, gastrointestinal disturbances, adrenal insufficiency, headache, and hyperandrogenism. Symptoms may alternative have been a result of glucocorticoid withdrawal syndrome in some patients. Approximately one-third of patients presented adrenal insufficiency highlighting the potency of osilodrostat. An increase of testosterone levels was seen in most patients that may traduce in hirsutism and acne in females.

Despite these promising results, a phase III study (LINC3) on a larger number of patients (137 patients with CD) followed for a longer period of time is ongoing to evaluate the real potential efficacy and safety of this novel adrenal-directed drug, as well as to determine whether patients will experience a late escape from response. After randomized withdrawal, osilodrostat was confirmed to be significantly superior to placebo in maintaining the normal UFC levels. Two-thirds of patients enrolled, presented normal UFC levels at 48 weeks of treatment. Cushing QoL and Beck depression inventory II scores also improved during treatment. In conclusion, osilodrostat demonstrated good efficacy and a satisfactory safety profile showing to be a promise treatment for patients with CD.

Receptor antagonists

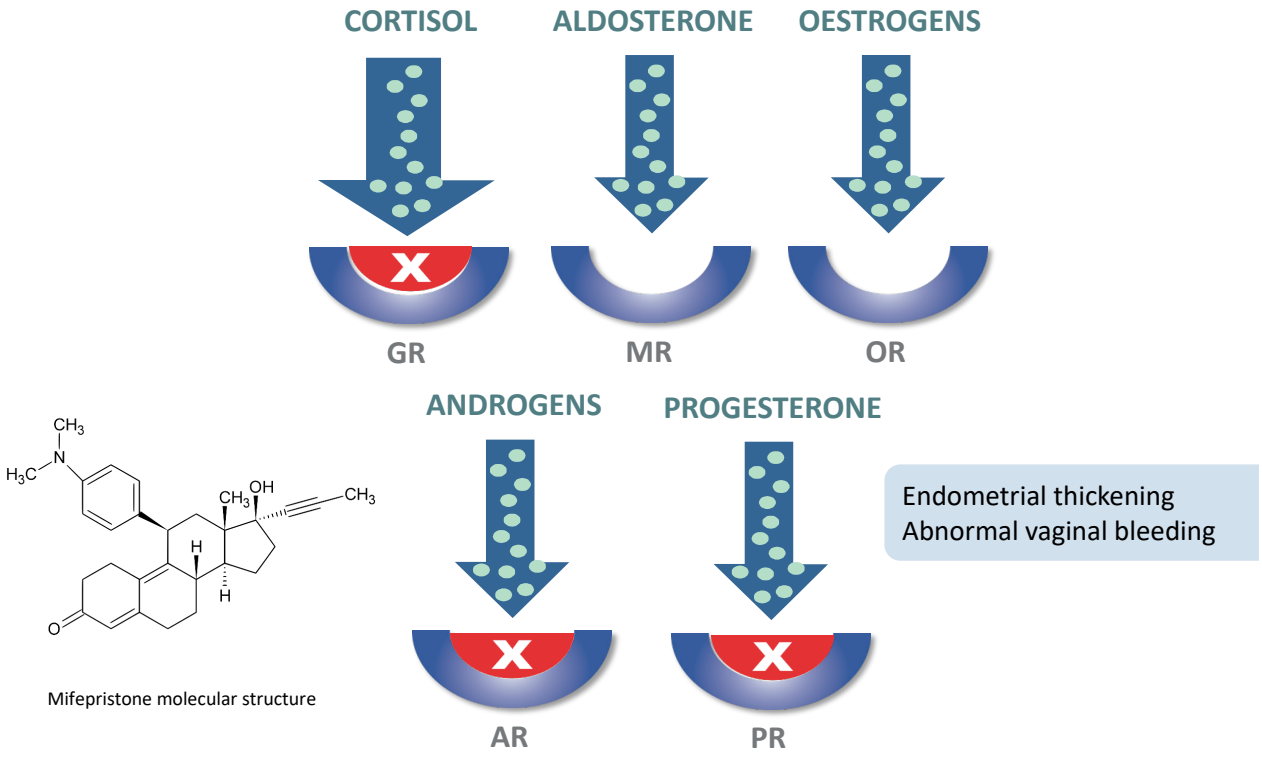
MIFEPRISTONE

GR antagonists antagonize cortisol effects by blocking GRs. The only currently available compound is Mifepristone (RU 486), discovered in the early 1980s, that acts by blocking central and peripheral type II GR, and consequently antagonizing cortisol receptor binding. The compound was officially approved in 2012 in the United States Food and Drug Administration for the treatment of patients suffering from CS associated with diabetes mellitus or impairment of glucose tolerance, who are not surgically treatable or have not been cured by surgery. Due to its mechanism of action, plasma ACTH and serum cortisol levels cannot be used as efficacy parameters, by limiting the evaluation of drug efficacy to clinical parameters. Mifepristone, orally administered at a dosage of 300–1200 mg once daily, has shown efficacy rates up to 87%, in terms of clinical picture improvement, including decrease in body weight, waist circumference, and body fat and increase in insulin sensitivity. Moreover, 60% of patients improved diabetes mellitus or impaired glucose metabolism, and 38.1% improved hypertension.

However, the experience in the treatment of CS is limited. Eighteen case-reports and one retrospective study including 20 patients indicated that mifepristone use may lead to significant clinical improvement in patients with uncontrolled hypercortisolism. There is only one clinical trial specifically designed to explore safety and efficacy of mifepristone in patients with CS. In SEISMIC trial, a 24-week open-label phase III study, 50 subjects were included. Among type 2 diabetes mellitus/impaired glucose tolerance patients, 60% responded with significant improvements in glycaemic control and 38% of hypertensive patients had a reduction in diastolic blood pressure. 52% of patients lost at least 5% of their baseline weight, and 26% lost at least 10%. The mean oral dose of mifepristone was 732 ± 366 mg once-daily. Altogether 34 patients completed the study. Seven patients discontinued mifepristone because of an adverse event: the most common adverse events were nausea, fatigue, headache, peripheral edema, hypertension, endometrial hyperplasia, and hypokalemia. Adrenal insufficiency occurred in two patients and responded to withdrawal of mifepristone and dexamethasone administration. Some of patients that completed the SEISMIC study were enrolled in the long-term extension study (LTE). This study showed that in 80% of patients that lost ≥5 % and ≥10 % of body weight by the end of the initial 24-week treatment period, the weight loss persisted at LTE final visit (median treatment period of 29.2 months). Moreover, the LTE study confirms that in the majority of CD patients, treated for a median duration of 11.3 months, a 2-fold increase in ACTH occurs. However, ACTH elevation was observed within the first few weeks of treatment, was dose-dependent, generally remained stable overtime, and was unrelated to the tumor growth. No new safety signals were reported. Unfortunately, no long-term data are available about glycaemic control or hypertension.

Generally, as far as safety profile was concerned, the most important adverse events are represented by endometrial thickening (38.5%), due to the antagonism of mifepristone on progesterone and androgen receptors, hypokalemia (25–34%) and hypertension (24–25%), both due to the "spill-over" effect exerted by cortisol excess on MC receptors. Additional common adverse events include gastrointestinal disturbances, fatigue, headache, arthralgia, peripheral edema, adrenal insufficiency, and dizziness.

Mifepristone



Mifepristone molecular structure

GR: Glucocorticoid Receptor; MR: Mineralocorticoid receptor; ER: Oestrogen receptor; AR: Androgen receptor; PR: Progesterone receptor

PHASE III STUDIES ON RELACORILANT

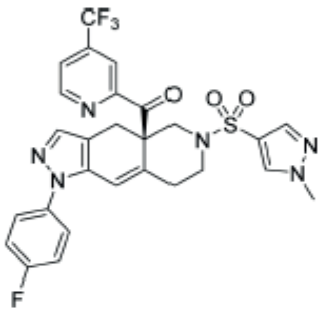
Relacorilant (CORT125134) is a new GR antagonist with a higher safety profile. In vitro studies showed that Relacorilant was GR selective, therefore potentially able to avoid the adverse events related to the anti-progestin effects of mifepristone. Moreover, in the same study Relacorilant was tested in a rat model of exogenous CS, identifying a significant positive effect on glucocorticoid-induced alteration in glucose metabolism, that were similar compared to mifepristone. Therefore, Relacorilant was considered as a potential candidate for clinical investigation and a Phase I study was performed on healthy volunteers. In this single center study on 81 healthy subjects, Relacorilant showed to be rapidly absorbed, with an half-life of about 12-14 hours, although a delay in absorption was observed after food intake. Moreover, Relacorilant presented a good safety profile, with musculoskeletal, connective tissue and gastrointestinal disorders being the most commonly reported adverse events after both single dose and multiple doses administration.

Due to the positive pre-clinical and Phase I evidences, a Phase II, multicenter, open-label clinical trial on the effects of Relacorilant treatment on CS patients, started in June 2016 and was completed by September 2018. In this study, 35 CS patients, of which 28 suffering

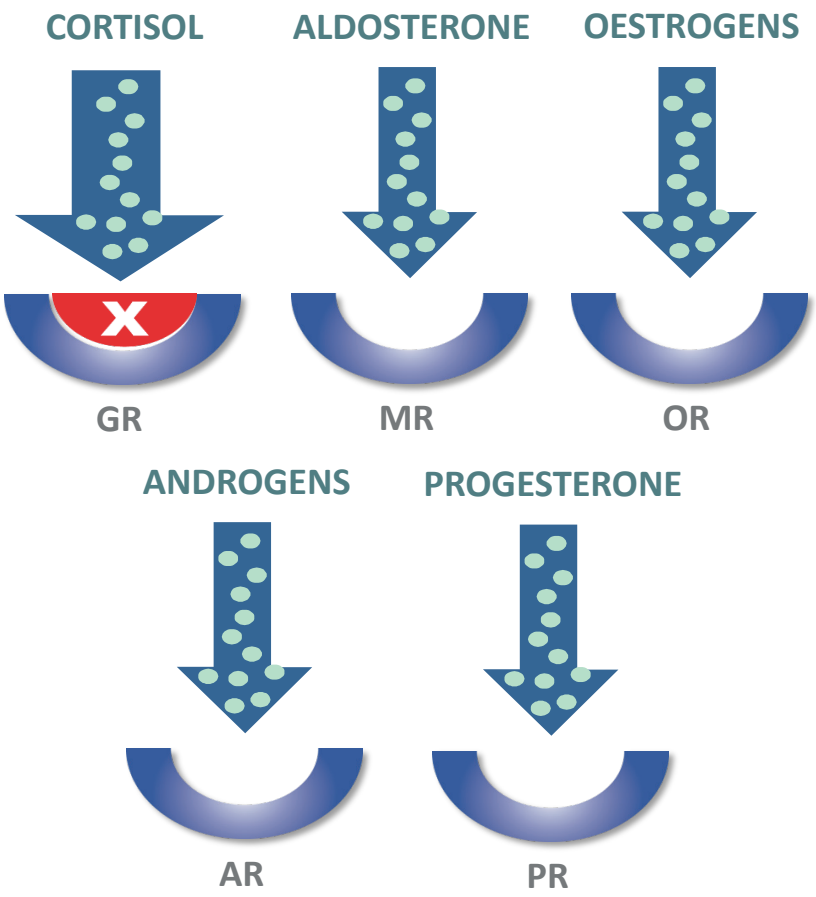
from CD, were enrolled and divided into two cohorts: in the first one, starting dose was 100 mg/day, slowly escalated to a maximum of 200 mg/day (Low Dose LD patients), whereas in the second one starting dose was 250 mg/day, slowly escalated to a maximum of 400 mg/day (High Dose HD patients). In both cases, escalation dose was 50 mg/day every 4 weeks. After 4 weeks of treatment at stable doses, Relacorilant was able to induce an improvement in blood pressure levels in 41.7% and in 63.6% of LD and HD patients, respectively, whereas an improvement in glucose metabolism was observed in 15.4% and in 50% of LD and HD patients, respectively. Moreover, a reduction in body weight was observed in 35.3% and 60% of LD and HD patients, respectively, and an overall improvement in scores regarding neurocognitive functions, depressive status, and QoL was reported. Furthermore, an improvement in coagulative status, hepatic function, and immune system activity was observed. Focusing on safety profile, the most commonly reported adverse events were back pain (31.4%), headache (25.7%), and peripheral edema (25.7%), with an higher prevalence in the HD patients compared to LD patients. In the HD patients group, five serious adverse events, including pilonidal cyst, myopathy, polyneuropathy, myocardial infarction, and hypertension, were reported. Noteworthy, no cases of hypokalemia or vaginal bleeding were observed.

Currently, a Phase III, multicenter clinical trial to assess the efficacy of Relacorilant in CS patients is ongoing in North America and Europe. The primary endpoint of this study is to assess the improvement in glucose alteration metabolism and in arterial hypertension, as compared between Relacorilant and placebo treatment in the randomization phase, and to evaluate the safety profile of Relacorilant throughout the study.

Relacorilant



Relacorilant molecular structure



GR: Glucocorticoid Receptor; MR: Mineralocorticoid receptor; ER: Oestrogen receptor; AR: Androgen receptor; PR: Progesterone receptor

Conclusion

In recent years, the role of medical treatment has significantly increased, particularly in CD management, being a suitable choice as pre-surgical or post-surgical treatment, in case of unsuccessful pituitary surgery, as bridging treatment before and after the administration of radiotherapy while awaiting its definitive effects, and as primary treatment in case of severe disease, lack of indications, or contraindications, and in case of refusal of surgery and/or radiotherapy.

Different categories of drugs have been used, including pituitary-directed drugs, mainly pasireotide and cabergoline, adrenal-directed drugs, mainly including ketoconazole and metyrapone, and the GR antagonist mifepristone. Among adrenal directed drugs, new compounds, levoketoconazole and osilodrostat, as well as a new selective GR antagonist, relacorilant, are under investigation.

Currently, the availability of different drugs has raised the possibility of combined treatment aimed at improving the endogenous hypercortisolism control, compared with monotherapy, particularly by using different drugs acting at different levels, and to improve safety profile, particularly by using lower doses compared to those classically used in the monotherapy. Nevertheless, further studies on larger populations of patients are needed to evaluate clinical advantages, in terms of drug benefits and side effects.

IL DOCUMENTO DERIVA DAGLI INTERVENTI DEL SIMPOSIO
“NOVITÀ IN TEMA DI TERAPIA MEDICA DELLA SINDROME DI CUSHING”
SVOLTOSI A NAPOLI IL GIORNO 11 DICEMBRE,
NEL CORSO DELL’EVENTO FORMATIVO ABC 2019.

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