Medical Therapies of Cushing's Disease–Part 1

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KEYWORDS

• Cushing's disease • Cushing medications • Corticotroph adenoma
• Cushing second line therapy • Medical therapy • Steroidogenesis inhibitors

KEY POINTS

- Cushing's disease is a severe endogenous hypercortisolism disorder.
- Medical therapy is an important second line therapy for Cushing's disease.
- Current medications target the corticotroph adenoma, adrenal steroidogenesis, and glucocorticoid receptors.
- Selection of suitable medications depends on patient's specific characteristics and medications effectiveness as well as adverse effects.

INTRODUCTION

Cushing's disease (CD), caused by an adrenocorticotropic hormone (ACTH) secreting pituitary tumor, is the most common form of endogenous hypercortisolism (Cushing's syndrome [CS]).[1,2] It is a rare disease with a global prevalence of 2.2/100,000 persons with female predominance.[3,4] On long-term follow up, patients with CD had poorer health-related quality of life, compared with patients with adrenal related cause of CS.[5] Transsphenoidal surgery (TSS) is the first line recommended treatment for CD[2,6] with remission rates after first TSS of approximately 83% (microadenoma)

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Abbreviations	
ACTH	Adrenocorticotropic hormone
AE	adverse effects
bid	twice a day (medication dosage)
CD	Cushing's disease
CS	Cushing's Syndrome
D2	Dopamine receptor type 2
EGFR	Epidermal growth factor receptor
EMA	Europeans Medicines Agency
ESE	European Society of Endocrinology
FDA	United States Food and Drug Administration
GR	Glucocorticoid receptor
HDAC	Histo deactelylases
HPA	Hypothalamic Pituitary Adrenal
HSP90	Heat shock proten 90
LNSC	late night salivary cortisol
SEISMIC	Study of the Efficacy and Safety of Mifepristone in the Treatment of Endogenous Cushing Syndrome
sstr	Somatostatin receptor
TSS	Transsphenoidal surgery
UFC	Urinary free cortisol
ULN	upper limit of normal

and 68% (macroadenoma), and long-term recurrence rate between 17% and 30% depending on the size and presurgical visibility of the tumor and neurosurgical expertise.[7] Medical therapy for CD is indicated in cases for whom surgery is unfeasible or incurable, cases of postsurgical persistent or recurrent disease and as a bridging therapy prior to surgery or after radiotherapy.[7] Medical therapy in CD aims at normalization of cortisol concentrations, reduction of comorbidities as well as improvement of patients' quality of life.[7] The rate of medical therapy utilization is highly variable between different medical centers with a range of 4.8% to 82.9%,[8] with an approximate cortisol normalization rate of 49.4% to 59.5% in CD.[9] Currently existing drug classes are directed either at the pituitary tumor, adrenal steroidogenesis, or at the glucocorticoid receptor (GR) itself.[2] This article is divided into two parts–part 1 focuses on recent updates concerning available pharmacologic therapy of CD, part 2 focuses on implications of long-term medical therapy, practical information regarding tailored medical treatment of CD novel targets and treatments under development. An overview of the available medical therapies discussed in this part of the article alongside their mode of action, approval, recommended dosing, and common side effects is provided in **Table 1**.

PITUITARY TARGETED MEDICAL THERAPY

The category of pituitary targeted medical therapy for CD includes dopamine and somatostatin receptor agonists as well as alkylating drugs.[10] Other potential treatments include check point immune inhibitors[11] and cyclin-dependent kinase inhibitors.[12]

Dopamine Agonists

The majority of ACTH-secreting pituitary tumors expresses dopamine receptor subtype 2 (D2).[13,14] The efficacy of dopamine agonists monotherapy for CD treatment is moderate with about 34% remission rate and 22% escape rate,[15,16] and was mostly studied in small prospective or retrospective studies utilizing cabergoline.[15–23]

Table 1
Overview of mechanism of action, approval, recommended dosing, and common side effects in current medications used for the treatment of Cushing's disease

Medication	Mechanism of Action[a]	Approval for CS	Recommended Dosing	Common Side Effects[b]
Adrenocorticotrophic adenoma directed medications				
Dopamin agonists (Cabergoline)	Agonist to dopamine receptor type 2	Off-label use	1–7 mg/wk	Nausea, headache, orthostatic hypotension, personality change
Pasireotide	Multi target somatostatin analogue	FDA EMA	S.C 0.6–0.9 mg/bid I.M 10 or 30 mg monthly	Cholelithiasis, hyperglycemia, hypocortisolism, QT prolongation
Temozolomide	Alkylating agent	Off-label use	5 d cycle with 28 d between cycles	Liver toxicity, myelosuppression, immunodeficiency
Steroidogenesis inhibitors				
Ketoconazole	Inhibition of CYP11A1, CYP11B1, CYP11B2, CYP17A1	EMA	200–1200 mg/day, divided in 2 (-3) doses	Liver toxicity, male hypogonadism, drug–drug interactions
Levoketoconazole	CYP11A1, CYP11B1, CYP11B2, CYP17A1, and further enzymes	FDA	300–1200 mg/day, divided in 2 doses	Nausea, headache, fatigue, edema, hypertension; liver toxicity and drug-drug interactions less common compared to ketoconazole
Metyrapone	CYP11B1, CYP11B2	EMA	500–6000 mg/d, divided in 3–4 doses	Hypertension, female hirsutism or acne, edema, hypokalemia
Osilodrostat	CYP11B1, CYP11B2,	EMA FDA[c]	2–60 mg/d, divided in 2 doses	Nausea, fatigue, headache, diarrhea, QT-prolongation

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Table 1
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Medication	Mechanism of Action[a]	Approval for CS	Recommended Dosing	Common Side Effects[b]
Etomidate	CYP11A1, CYP11B1, CYP17A1	Off label use	0.1 mg/kg/day, continuous infusion	Thrombophlebitis, pain on injection, nephrotoxicity, lactic acidosis
Glucocorticoid receptor antagonists				
Mifepristone	Non-selective GR antagonist with anti-progesterone effect	FDA for hyperglycemia in endogenous CS	300–1200 mg/d	Hypokalemia, QT prolongation progesterone-related vaginal bleeding, endometrial thickening
Relacorilant	Selective GR modulator; minimal progesterone affinity	Investigational; phase 3 trial completed	Definite recommended dose not yet determined	Mild adverse effects including back pain, headache, arthralgia, insomnia; No endometrial changes reported; limited long-term data

Abbreviations: AI, adrenal insufficiency; CS, Cushing's syndrome; EMA, European Medicine Agency; FDA, Food and Drug Administration; GR, glucocorticoid receptor.

[a] Adrenal steroidogenesis inhibitors mechanism of action is based on inhibition of glucocorticoid synthesis pathways. Specific inhibited enzymes are mentioned in the table.

[b] Adrenal insufficiency is a potential side effect of all steroidogenesis inhibitors. It is very common in etomidate, common in osilodrostat and metyrapone and less common in ketoconazole and levoketoconazole.

[c] As of 03.2025 osilodrostat holds FDA approval for endogenous Cushing's syndrome in cases for whom surgery is not possible or has not been curative.

Suggested dosage range of Cabergoline lies between 0.5 and 7 mg/wk,[2] with lower dosages in cases of combination therapy of cabergoline and steroidogenesis inhibitors.[23] Cabergoline treatment is usually well tolerated with mild adverse effects (AEs) in 37.3% and severe AEs among 5.6% of the patients.[15,16] The most common AE of cabergoline included nausea (13.5%) while severe AEs such as personality change (0.8%), hypocortisolism and hypotension (5 and 2 patients in one metanalysis) were exceedingly rare.[15,16] Cabergoline was studied as possible combination therapy with different medications including ketoconazole with improved control rate from 25% to 75%,[20] pasireotide with improvement of control rate from 25% to 50%,[24] and combination of ketoconazole, cabergoline, and pasireotide.[25] Currently there is no specific sequence of treatment recommended regarding ketoconazole and cabergoline.[21] The role of preoperative treatment of patients with CD is still debated especially due to the less severe nature of CD compared to extra pituitary CS,[26] and cabergoline is seldomly used for this purpose.[27] The effectiveness of presurgical cabergoline therapy is unclear with only one small study who failed to achieve normalization of urinary free cortisol (UFC) in presurgical patients compared with 43% normalization of UFC in postsurgical patients with recurrent disease.[28]

Somatostatin Analogues

Somatostatin is an important regulator of hormonal secretion, exerting its effects by binding to specific membranous G-protein coupled somatostatin receptors, of which 5 isoforms exists (sstr1-5).[14] Currently two generations of somatostatin receptors analogues (SSTa) are being used in clinical practice, first generation SSTas include octreotide and lanreotide which exert their effect mainly via sstr2 while second generation SSTas include the multi receptor targeted pasireotide, which exerts its function mostly via sstr5.[29] Expression of sstr5 in corticotropic tumor cells is about 5 to 10 times higher than that of sstr2, which is explained by selective downregulation of sstr2 expression by exposure of the cells to high levels of glucocorticoids.[30,31] The observed upregulation of sstr2 in corticotroph tumors after cortisol-lowering therapy[32] the positive effect of octreotide on pituitary tumors in patients with Nelson's syndrome after bilateral adrenalectomy albeit not widely studied,[33] have led to a trial of sequential therapy using ketoconazole as first treatment to normalize cortisol concentrations, after which octreotide was given as a maintenance treatment, with 3 of 11 of study participants maintaining normal UFC and 4 of 11 defined as partial responders.[31] This study demonstrated a possibility of a sensitizing sequential regimen as a therapy for CD.[31]

In 2012, pasireotide bid was approved for the treatment of CD by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA). In the phase 3 study 15% to 26% (600 and 900 μcg, respectively) of study participants had normalized UFC by 6 months of treatment[34] and long-term efficacy was demonstrated in a 5 years long open label extension of the study showing preservation of median UFC change between 12 and 60 months of treatment.[35] Subsequent analysis demonstrated clinical association of UFC reduction and improvement of hypercortisolism associated comorbidities.[36] Real world studies showed varied degrees of UFC normalization between 37.5% and 80% but differed in follow-up time as well as severity of pretreatment hypercortisolism among the different studies participants.[37,38] Once monthly intramuscular pasireotide LAR was approved in 2018 with 40% of the patients in each treatment arm of the phase 3 study (10 or 30 mg) reaching normal UFC by 7 months. Long-term efficacy was shown in an open label extension study.[39] In one real-world study of pasireotide LAR, UFC normalization was achieved in 53% of, patients.[40] In another small real-world study, a complete biochemical response

(ie, normalization of UFC and late night salivary cortisol [LNSC]) was observed in 3 of 6 patients, while 2 of 6 patients achieved UFC normalization but showed continuously elevated LNSC, which eventually led to pasireotide discontinuation.[41]

In both phase 3 studies UFC reduction among patients who responded to treatment occurred after 1 to 2 months, and baseline UFC concentrations were negatively correlated with achievement of disease control.[34,42] Pasireotide has also an effect on tumor volume with shrinkage of tumor volume during treatment. A post hoc analysis of the phase 3 study pasireotide bid showed 9.1% and 43.8% tumor volume reduction in patients treated with 600 and 900 bid, respectively,[43] while real-world studies showed lower incidence of tumor reduction (20%–25%).[38] In the phase 3 study of pasireotide LAR, median tumor volume in macroadenomas decreased by 11.6% to 14.6% and 16.3% to 17.8% in microadenomas, regardless of median UFC concentrations.[42] The most common pasireotide-related AEs (see **Table 1**) include gastrointestinal and biliary complaints as well as hyperglycemia.[24,34,35,39] Hyperglycemia, caused by decreased incretin and insulin secretion, will affect 40% to 50% of patients with varying severity–from new onset prediabetes or diabetes to worsening of existing diabetes.[24,34,42] Metformin is suggested as first line treatment for pasireotide induced hyperglycemia followed by incretin based medications.[44] Other common AEs include diarrhea (39%–58%) and cholelithiasis (30%–33%).[34,42] Hypocortisolism-related AEs were more rare (8%–9%) and in most cases improved with dose reduction,[34,42] while new QT prolongation occurred in 2% of the patients.[34]

Temozolomide

Temozolomide, an oral second-generation alkylating agent, is the first line chemotherapeutic agent recommended by the European Society of Endocrinology (ESE) guidelines for the treatment of aggressive pituitary adenomas and carcinomas.[45] Temozolomide is administered orally, is able to cross the blood–brain barrier and is not specific to cell cycle.[46] Temozolomide exerts its effect by attaching methyl group to guanine bases causing DNA mispairing leading to apoptosis. High tumoral content of O^6-methylguanine DNA methyl-transferase, a DNA repair enzyme might confer resistance to temozolomide[11] and expression of DNA mismatch repair proteins may be also important for the cytotoxic effects of temozolomide.[45] Evidence regarding the effectiveness of temozolomide in CD resistant to other treatment is scarce. A literature review done for the latest ESE guidelines for the treatment of aggressive pituitary adenomas and carcinomas suggests an objective response (ie, complete or partial response) in 37% of the patients, while 29% to 100% of patients with hyperfunctioning tumors showed decrease or normalization of hormonal concentrations without specific referral to ACTH-secreting tumors.[45] In a report including a large cohort of patients with aggressive pituitary adenoma or pituitary carcinoma, 33.6% of the patients with hyperfunctioning tumors achieved at least 50% reduction of secreted hormone concentrations.[47] Another review article including 34 cases of ACTH tumors found in 56% objective response and in 15% disease stabilization.[48] Currently, there is paucity of data regarding usage of biomarkers to predict response rate to temozolomide treatment, and current guidelines suggest treatment trial with temozolomide without regard to different biomarkers.[45] Temozolomide-related AEs are mostly mild but frequent (about half of the patients) and include fatigue and nausea/vomiting, and about third of the patients develop myelosuppression requiring dose reduction or cycle delay.[45] Increased risk for opportunistic infections is seen in patients receiving temozolomide and glucocorticoids (or with endogenous CS), and prophylactic antibiotic treatment for pneumocystis pneumonia should be considered in cases of significant lymphopenia.[45]

STEROIDOGENESIS INHIBITORS

Adrenal steroidogenesis inhibitors comprise a group of drugs that inhibit one or more enzymes involved in steroidogenesis (**Fig. 1**). They represent the most effective and commonly used medical treatments for hypercortisolism and are characterized by a rapid onset of action. Currently, the drugs available for clinical use in patients with CD include ketoconazole, levoketoconazole, metyrapone, osilodrostat, and etomidate.[49] Steroidogenesis inhibitors may be applied alone or on combination as well as in a titration or a block-and-replace approach. The choice of drug depends on availability, as not all of them are globally accessible, as well as individual patient profiles[50] (see part 2 for "Tailored pharmacologic treatment"). Due to the risk of adrenal insufficiency it is strongly advised that all patients receiving steroidogenesis inhibitors be informed about the signs and symptoms of adrenal insufficiency and sick day rules, have access to both oral and injectable glucocorticoid replacements, and can consult specialist care when needed.[51] The following section provides an overview of their mode of action, approval, efficacy, dose adjustments, and common side effects (see **Table 1**).

Ketoconazole and Levoketoconazole

Both ketoconazole and its stereoisomer levoketoconazole are imidazole derivates that inhibit key enzymes involved in adrenal steroidogenesis, including CYP11A1, CYP17A1, CYP11B1, and CYP11B2.[52,53] Levoketoconazole shows higher *in vitro* potency and longer half-life (~4–6 h) than ketoconazole (~3.3 h).[53–55] Ketoconazole is approved by the EMA, but not the FDA, for CS in patients of 12 years or more. Levoketoconazole has FDA approval for adult patients with CS unsuitable for surgery and holds an orphan drug indication in Europe. Ketoconazole is typically administered at 200 to 1200 mg/day in 2 to 3 divided doses,[52] with UFC control usually at 600 to 800 mg/day. It requires an acidic gastric environment for absorption.[52,56] Levoketoconazole offers improved bioavailability and is dosed at 150 to 600 mg twice daily

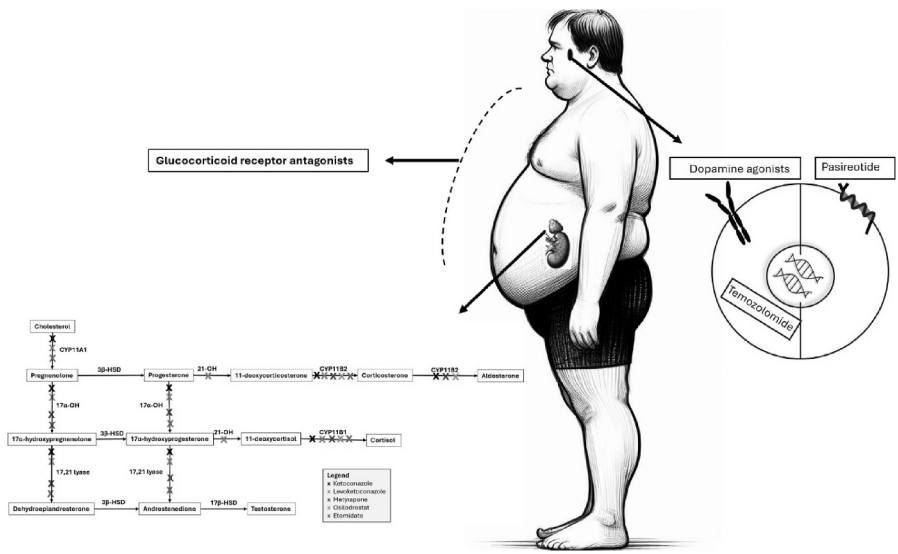

Fig. 1. Current available medications for Cushing's disease. (Created using Microsoft Designer software.)

(up to 1200 mg/day), allowing lower total doses and potentially reducing dose-related toxicity.[54]

Ketoconazole has shown normalization of UFC in 49% to 66% of patients with CD within approximately 4 months in retrospective studies,[56,57] with similar response rates reported in larger meta-analyses.[9,58] However, treatment escape has been described in 7% to 23%.[59] For levoketoconazole, the SONIC study demonstrated UFC normalization in 81% of patients during the titration phase,[60] with sustained control in 41% to 61% over 6 to 12 months.[61] The LOGICS study showed that 50% of patients treated with levoketoconazole achieved UFC normalization, compared to 5% of patients receiving placebo.[62]

Both drugs carry a risk of hepatotoxicity, although levoketoconazole may have a lower incidence.[53] Mild-to-moderate liver enzyme elevations are common and reversible with both. Ketoconazole more commonly causes male hypogonadism due to androgen suppression, while levoketoconazole has less impact on testosterone concentrations. QT-prolongation occurs with both (up to 5% for levoketoconazole).[60]

Nausea, headache, and fatigue are frequent side effects of levoketoconazole, while ketoconazole also commonly causes gastrointestinal symptoms and skin rash. Drug–drug interactions via CYP3A4 inhibition are relevant for both agents, though ketoconazole is more prone to broader interactions.[52,53]

Metyrapone

Metyrapone, a pyridine derivative, inhibits CYP11B1 and CYP11B2.[63] Although it is approved by the EMA for the treatment of CS, its use for this indication remains off-label in the United States, where the FDA has approved it only for adrenal function testing. Metyrapone is administered orally in typical doses of 500 to 6000 mg/day. Due to its short half-life of approximately 2 hours, it is administered 3 to 4 times a day.[50] The short half-life also makes it a useful drug in chronotherapeutic treatment approaches, where it is usually administered in the late afternoon and before nighttime.[50]

The multicenter open-label PROMPT trial has prospectively evaluated the efficacy of metyrapone. In this study, UFC was normalized in 47% of patients with CS (n = 50) at 12 weeks on a median final dose of 1500 mg/day, with 80% of the patients experiencing a UFC reduction of greater than 50%.[64] Further data on efficacy and safety derive from retrospective studies, with a meta-analysis reporting biochemical control (ie, UFC < ULN) in up to 76% of patients, though study designs varied widely.[9] Larger studies (n = 195) suggest lower biochemical control rates (~43%),[65] while smaller ones (n = 31) report up to 70%.[66] Compared to osilodrostat, metyrapone may be less potent and slower-acting,[67] though data are limited, and prospective head-to-head trials are missing.

When assessing the effect of metyrapone, it is important to acknowledge that some older immunoassays may overestimate cortisol concentrations due to its cross-reactivity with 11-deoxycortisol. Consequently, biochemical monitoring of metyrapone should be performed by means of adequate immunoassays or mass spectrometry.[68]

Adverse events associated with metyrapone are usually reversible and relate to the ACTH-induced increase in mineralocorticoid and androgen precursors. In female individuals, this may lead to hirsutism and acne in 5% to 71%. Further side effects independent of sex, include hypertension in up to 48% of patients, edema in 3% to 23%, and hypokalemia in 7% to 14%.[9,65]

Osilodrostat

Like metyrapone, osilodrostat inhibits CYP11B1 and CYP11B2, but with a longer half-life (~4 hours) and, potentially, a higher *in vitro* potency for inhibition of CYP11B1.[69] It

also partially inhibits CYP17A1 and CYP21A2, potentially leading to fewer androgen-related side effects in women.[70] Osilodrostat is approved by the FDA for CD and by the EMA for all etiologies of CS. It is administered orally at doses of 2 to 60 mg/d, typically twice daily,[70] although a small recent pilot study indicated that its once daily evening use may also improve physiologic cortisol rhythm in patients that have previously been well controlled on osilodrostat twice daily.[71]

Efficacy and safety of osilodrostat in patients with CD have been and are ongoingly evaluated by the LINC trials.

- *LINC-1:* UFC normalization in 11/12 (92%) patients with CD at 10 weeks[63]
- *LINC-2*: UFC normalization in 15/19 (79%) patients with CD at 22 weeks[72]
- *LINC-3*: In a double-blind randomized withdrawal phase, 31 of 36 (86%) patients on osilodrostat maintained UFC normalization versus 10 of 34 (29%) patients on placebo at week 34.[73] At week 72, 86 of 106 (81%) maintained normal UFC[74]
- *LINC-4*: In milder CD, 37 of 48 (77%) achieved UFC normalization versus 2/25 (8%) on placebo[75]
- A pooled analysis (n = 210) showed improvements in comorbidities: 54 of 110 (49%) normalized systolic blood pressure and 16 of 26 (62%) HbA1c in patients with elevated baseline values at 72 weeks.[76] Normalization of both UFC and LNSC was associated with a more pronounced improvement in comorbidities compared to normalization of UFC alone, highlighting the importance of recovery of cortisol diurnal rhythm.[69]

Due to potential cross-reactivity with 11-deoxycortisol–as in metyrapone–biochemical monitoring should be performed with suitable immunoassays or mass spectrometry.[77] Adrenal insufficiency has been reported to occur in approximately 30% of patients. Consequently, patients receiving osilodrostat need to be educated and equipped with glucocorticoid replacement as a precaution. Further adverse events include fatigue, nausea, headache, diarrhea, hypokalemia, edema, hypertension, QT-prolongation, and mild transaminase elevations.[63,72,73] Prolonged adrenal insufficiency after osilodrostat withdrawal has been described in several case reports[78]; however, the underlying mechanisms remain unclear.

Etomidate

Etomidate is a short-acting intravenous agent that inhibits CYP11B1, as well as CYP11 A and CYP17A1, leading to rapid suppression of cortisol production within 12 to 24 hours.[79,80] It is not officially approved for CS but used off-label by both EMA and FDA. It is primarily used in cases of severe hypercortisolism, particularly in critically ill patients requiring intensive care or those unable to take oral medications. A recent systematic review article of 76 cases with severe CS from different etiologies and 78 clinical episodes of etomidate use reported a median time to lowest cortisol of 38 hours (range: 3–264 hours), with 81% of patients surviving to receive definitive therapy.[81] Data on optimal dosing are scare; however, case reports suggest that doses 0.1 mg/kg/h or less are generally effective.[82] A commonly used intensive care protocol involves a 5 mg bolus administered over 2 to 3 minutes, followed by a continuous infusion starting at 0.02 mg/kg/h, titrated in 0.01 to 0.02 mg/kg/h steps every 6 hours (maximum infusion rate 0.3 mg/kg/h) based on serum cortisol concentrations.[83,84]

Both ethanol-based and propylene glycol-based formulations are available. Propylene glycol formulations may be associated with injection-site pain, thrombophlebitis, nephrotoxicity, and lactic acidosis at high doses.[80,85] Sedation is uncommon at the doses typically used for cortisol suppression.[81] Given its high potency and the

frequent occurrence of adrenal insufficiency, a block-and-replace strategy with glucocorticoids is often considered more convenient.[80]

GLUCOCORTICOID RECEPTOR ANTAGONISTS

GR antagonism can be a therapeutic strategy in the management of CD, particularly for patients with persistently elevated cortisol concentrations who are not candidates for or have failed surgery.[6] Unlike steroidogenesis inhibitors that reduce cortisol synthesis, GR antagonists block cortisol action at the receptor level, offering an alternative mechanism to mitigate end-organ effects of hypercortisolism.[10,86] Two orally administered GR modulators, mifepristone and relacorilant, have been evaluated in prospective studies of patients with CS.[86–88] Overview of mechanism of action, approval status, recommended dosage, and common side effects is provided in **Table 1**.

Mifepristone

Mifepristone, a non-selective GR antagonist with anti-progesterone activity, was the first FDA-approved medical therapy for endogenous CS. The Study of the Efficacy and Safety of Mifepristone in the Treatment of Endogenous Cushing Syndrome (SEISMIC) trial, a 24 week multicenter, open-label study, demonstrated that mifepristone significantly improved glycemic control and blood pressure in patients with glucose intolerance or diabetes mellitus and hypertension.[86] Clinically significant improvement was reported in 87% of patients.[86] Depression, cognition, and quality of life also improved in patients over the course of 24 weeks.[86,89] Notably, the response was dose-dependent, with greater improvements in metabolic parameters observed at higher doses.[90] Long-term extension data showed sustained clinical benefits over 24 months in weight loss and body composition.[91] AEs related to progesterone receptor antagonism such as endometrial thickening and vaginal bleeding in women, symptoms of cortisol insufficiency (fatigue, nausea, vomiting, arthralgias, and headaches), and evidence of increased mineralocorticoid action (hypertension, hypokalemia), and QT prolongation have been reported.[6,86,92] The most common AEs in the SEISMIC included hypokalemia (44%), endometrial thickening (38% of women), and reversible TSH elevation (19%).[10,86] Furthermore, mifepristone treatment causes disinhibition of the hypothalamic–pituitary–adrenal axis by inhibiting negative feedback, and this results in higher levels of circulating ACTH and cortisol.[93] While many of these effects are reversible and manageable with dose titration and close monitoring, the absence of a biochemical marker of treatment response remains a challenge.[94,95]

Relacorilant

Relacorilant is a selective GR modulator with minimal affinity for the progesterone receptor, potentially mitigating off-target effects. In line with preclinical data, relacorilant does not cause ACTH or cortisol elevations of the same magnitude seen with mifepristone, which may explain the absence of drug-induced hypokalemia and greater blood pressure-lowering effects seen with relacorilant.[88,96] A favorable hepatic safety profile was demonstrated in a dedicated study of patients with liver impairment,[97] and its ability to reverse cortisol-mediated immunosuppression has been shown in preclinical and translational studies.[98] In the Phase 3 GRACE trial, patients with endogenous CD and impaired glucose metabolism and/or hypertension were treated with relacorilant for 22 weeks, followed by a 12 week randomized withdrawal phase.[88,99] Patients continuing relacorilant were significantly more likely to attain blood pressure control

compared to those switched to placebo. Sustained improvements in hypertension and hyperglycemia were observed during relacorilant treatment.[100] In an open-label extension study, reductions in systolic and diastolic blood pressure, body weight, and glycemic control were sustained for up to 24 months.[101–103] The most commonly reported AEs were back pain, headache, arthralgia, insomnia, and extremity pain, which were generally mild to moderate in severity.[100] Importantly, no cases of adrenal insufficiency, QT interval prolongation, or endometrial thickening with vaginal bleeding were observed.[100] A summary of the characteristics of mifepristone is provided in **Table 1**.

Role of Glucocorticoid Receptor Antagonists in Treatment

In the SEISMIC, 28% of patients required adjunctive spironolactone at doses up to 400 mg/day, supporting combination therapy in cases of mineralocorticoid-related toxicity.[86] Mifepristone has also shown efficacy comparable to bilateral adrenalectomy in ectopic ACTH-dependent hypercortisolism.[101–104] It was approved by the FDA in 2012 for the treatment of hyperglycemia due to hypercortisolism in patients with type 2 diabetes or glucose intolerance who have failed or are ineligible for surgery.[10] In current clinical practice, GR antagonists are indicated in patients with hyperglycemia in whom surgery is contraindicated or was unsuccessful, and as a short-term intervention for acute hypercortisolism (including cortisol-induced psychosis).[105,106] Mifepristone remains the more extensively studied agent, but relacorilant may offer a safer option, particularly in women of reproductive age and those with cardiometabolic risk factors. Results from the GRACE Phase 3 trial support relacorilant's efficacy and favorable safety profile, and further long-term data may guide its integration into future treatment algorithms. Until then, GR antagonists should be considered as a useful tool in the multidisciplinary management of CD, particularly when surgical cure is not feasible.[6]

SUMMARY

Medical treatment of CD is an important line of treatment for patients in whom curative surgical treatment is not feasible due to various causes.[2] Current available medical treatment for CD target various processes in CD pathophysiology from the pituitary tumor, to adrenal steroidogenesis pathways and the GR.[6] Effectiveness range of existing medical therapies in achieving normalization of UFC is wide, with lower rates of UFC normalization in the pituitary targeting drugs cabergoline and pasireotide (15%–40%)[15,16,34,42] and higher rates of UFC normalization for ketoconazole,[9,56,57] levoketoconazole,[61,62] metyrapone (49%–66%),[64,65] and osilodrostat reaching to around 80%.[63,72] Escape from treatment was described for some of the drugs including cabergoline (22%)[15,16] and ketoconazole (7%–23%).[59] The choice between different drugs for the treatment of CD in a specific patient depends not only on drug efficacy but also on various other factors. Part 2 of this article illustrates the various factors to be considered in the choice between different medical therapies for CD as well as long-term aspects of medical therapy and novel therapies under development.

CLINICS CARE POINTS

- Cushing's disease medical therapy targets various pathophysiological processes of the disease from the tumor itself to steroidogenesis pathways and glucocorticoid receptor.

- Response time to treatment differ between various medical options and should be taken into account when choosing therapy as well as during follow up.
- Combination therapy is an option for patients without satisfying response to treatment with one agent.
- Follow up for treatment efficacy in various drugs can be affected by their mechanism of action, ie, cross reactivity of 11-deoxycortisol in older immunoassays during metyrapone treatment.

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