Medical Therapies of Cushing's Disease–Part 2

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KEYWORDS

• Cushing's disease • Cushing medications • Cushing tailored therapy
• Novel treatment targets in cushing • Cushing disease new drugs

KEY POINTS

- Cushing's disease (CD) is a severe endogenous hypercortisolism disorder.
- Medical therapy is an important second-line therapy for Cushing's disease.
- Medical therapy is an option for long-term treatment in Cushing's disease for specific cases.
- Novel pharmacologic targets, as well as treatment protocols are under investigation and might offer better disease control in the future.

INTRODUCTION

Medical therapy for cushing's disease (CD) is a second-line therapy reserved for patients in whom surgery is non curative or non feasible for various reasons.[1] Current medical therapies for CD target different pathophysiologic aspects of the disease and differ from each other in terms of efficacy, adverse effects (AEs), improvement rate, administration way, cost and more, necessitating individualized approach in choosing a treatment for a specific patient.[2] Part 2 of this article describes the various aspects of tailored pharmacologic treatment, as well as the efficacy and safety of long-term pharmacologic treatment and novel treatments developed for CD.

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Endocrinol Metab Clin N Am 54 (2025) 627–635
https://doi.org/10.1016/j.ecl.2025.08.003 **endo.theclinics.com**

Abbreviations	
ACTH	Adrenocorticotropic hormone
AE	Adverse effect
CD	Cushing's disease
CS	Cushing's Syndrome
EGFR	Epidermal growth factor receptor
HDAC	Histo deactelylases
HSP90	Heat shock protein 90
UFC	Urinary free cortisol

TAILORED-PHARMACOLOGIC TREATMENT

Decision-making regarding pharmacologic treatment for CS depends on several factors. First, determining whether the patient suffers from CD or other etiologies of CS is critically important. Second, the clinical condition of the patient also plays a crucial role, as patients with severe CS require fast-acting pharmacologic treatment. Finally, possible side effects of each medication should be considered (effects on liver enzymes, glucose balance, interactions with other drugs, effects of hyperandrogenism or hypo-androgenism, potassium levels, electrocardiogram [ECG] QT interval, and so on). In the following section, we will outline a tailor made choice based on patient's characteristics. A summary of specific baseline characteristics and possible exacerbating medications is provided in **Table 1**.

Severe Cushing's Disease Requiring Fast Cortisol Reduction

In cases of severe to life-threatening CD requiring fast cortisol reduction—etomidate can be considered in hospitalized patients who require intensive care and who are unable to take oral medications.[3] With a 1 to 3 d treatment duration required for cortisol normalization, yet a high risk of adrenal insufficiency and a possibly sedative effect, etomidate can only be used when continuous monitoring of vital signs is performed and as a bridge for definitive therapy. Metyrapone and osilodrostat are also fast acting, with some reports of urinary free cortisol (UFC) arriving near normalization

Table 1
Specific baseline characteristics and possible exacerbation due to medical treatment

Specific Baseline Characteristics	Exacerbating Treatment
Uncontrolled diabetes	Pasireotide
Psychosis	Cabergoline
Uncontrolled HTN and\or hypokalemia	Metyrapone, osilodrostat, mifepristone
Hepatitis	Ketoconazole, levoketoconazole
QT prolongation	Ketoconazole, levoketoconazole, Pasireotide
Hyperandrogenism	Osilodrostate, metyrapone
Hypoandrogenism	Ketoconazole, levoketoconazole
Drug interactions	Mitotane, mifepristone, ketoconazole, levoketoconazole
Irregular vaginal bleeding	Mifepristone

within 2 w,[4,5] while levoketoconazole show UFC reduction within 1 mo.[6] Mifepristone has also a rapid onset of action and can be useful in patients with severe complications of hypercortisolism, for example, psychosis.[7]

Possible Treatment Side Effects

- QT prolongation—most pronounced with levoketoconazole and ketoconazole treatment[8] but can also occur under pasireotide treatment.[9]
- Hepatic damage—ketoconazole and levoketoconazole can increase liver enzyme levels, mostly in a reversible fashion.[6,10] However, other predisposition states for hepatitis or already elevated liver function tests should call for attention before selecting these treatments.
- Hypertension and potassium levels—both metyrapone and osilodrostat may induce or worsen hypertension and hypokalemia.[5,11] Mifepristone may also lead to hypertension and severe hypokalemia due to activation of the mineralocorticoid receptor by increased cortisol levels.[12,13]
- Hyperglycemia—can be exacerbated by pasireotide while it can improve with adrenal-directed interventions and with glucocorticoid receptor (GR) antagonists mifepristone and relacorilant.[13,14]
- Specific gender effect—under mifepristone treatment women may experience irregular vaginal bleeding and endometrial thickening due to its effect on the progesterone receptor, but less so under relacorilant treatment.[13]
- Hyper-androgenism, hypo-androgenism—ketoconazole and levoketoconazole—can lead to reduced testosterone concentrations and consequently induce or worsen hypogonadism in men,[6] while metyrapone and osilodrostat may increase testosterone concentrations in women.[11]
- Drug interactions—pronounced with mifepristone (requiring adjustments), and mitotane,[13,15] as well as ketoconazole and levoketoconazole, all of which requires careful review of other medications taken by the patient before prescribing.[1]

To conclude this section, currently there is no "one size fits them all" pharmacologic agent for all patients with CD with every medication carrying its own advantages, as well as disadvantages. Every medication should be chosen after integrating the various factors of a specific patient and giving each factor its correct weight. This approach requires vast acquaintance of the different pharmacologic agents by the treating physician, as well as holistic approach to the patient and close monitoring.

LONG-TERM MEDICAL TREATMENT OF CUSHING'S DISEASE

Patients with CD in whom trans-sphenoidal surgery is not successful or not feasible are often treated with radiotherapy or bilateral adrenalectomy as definitive treatment with only a supporting role for temporal medical treatment. Although radiotherapy and bilateral adrenalectomy are still a mainstay for the treatment of these patients, the introduction of new drugs for CD and recently published studies with prospective long-term efficacy and safety data of old and new drugs may lead to a paradigm shift toward chronic medical therapy as option for treatment of persistent CD in some patients.

Prospective long(er)-term studies have been published with osilodrostat, levoketoconazole, pasireotide, miferpristone and relacorilant. In the LINC-3 and LINC-4 studies with osilodrostat (see paragraph 3.3 on part 1 of this article), the core phase was followed by an extension study. In LINC-3, 72 patients completed the extension phase with median exposure duration of 130 w.[16] Efficacy evaluation at week 72 showed that 81.1% of patients had controlled-cortisol production. The extension

phase of the LINC-4 study, completed by 53 patients with a median osilodrostat exposure of 87.1 w, showed similar results.[17] Control of cortisol production, achieved in the core phase, was sustained in 72.4% to the end of the extension phase. In both. LINC-3 and LINC-4, no escapes were observed throughout the extension phase. The proportion of patients with improvements in physical symptoms, cardiovascular/ metabolic parameters, and quality of life observed in the core phases was maintained or increased. Hypocortisolism-related symptoms were the most common adverse events, predominantly during dose-titration in the core phase. In the extension studies, no new safety signals were observed and discontinuation rate because of side effects was low.

The SONICS study evaluated the efficacy and safety of levoketoconazole during 6 mo.[6] An additional 6 mo maintenance phase showed at month 9 and 12 sustained biochemical remission in 55% and 41% of patients, respectively.[18] This was paralleled by maintenance of earlier improvements in clinical and metabolic parameters. Importantly, during the extension phase no relevant hepatotoxicity or QTcF prolongation, both potential side effects of racemic ketoconazole, was observed.

Long-term data are also available on short-acting and long-acting pasireotide. A small study with pasireotide subcutaneous showed sustained biochemical control in 11 of 16 patients during 60 mo without new safety issues.[19] A 12-mo phase III trial with long-acting pasireotide long acting release (LAR) was followed by an extension study with a median treatment duration of 23.9 mo.[20] Thirty-nine out of 81 patients completed the extension study. 47% of patients had controlled-UFC concentrations at month 24 with sustained improvements in clinical symptoms and quality of life. Hyperglycaemia (23.5%) was the most common AE during the extension study, although this led to discontinuation in a low patient number (n = 3). Pasireotide is not an ideal drug for chronic treatment of patients in whom glucose regulation deteriorates after initiating treatment. This introduces or worsens a cardiovascular risk factor with the need for chronic antidiabetic treatment. But if glucose homeostasis remains unaffected, pasireotide can be used for prolonged treatment with the advantage of targeting the disease source. In addition, pasireotide can induce tumor shrinkage, as was also shown in this extension study, and can be useful when control of tumor growth is needed.

Retrospective studies on prolonged treatment with metyrapone[5] and ketoconazole[10] demonstrated a reasonable efficacy without new safety signals. Finally, for both mifepristone and relacorilant efficacy and safety data are available from extension studies, with follow-up until 24 mo, demonstrating sustained improvements in body composition, blood pressure regulation, and glucose homeostasis.[21–24]

The choice for long-term medical treatment of CD patients who cannot be cured by surgery should be made in a tailor-made fashion with outweighing the (dis)advantages of radiotherapy and bilateral adrenalectomy. Both can provide definitive cure, although radiotherapy has a delayed onset of action and is not effective in a subset of patients. Adverse events of radiotherapy include the risk on hypopituitarism, cranial neuropathies, atherosclerosis, and secondary brain tumors, whereas bilateral adrenalectomy is accompanied by a risk on developing Nelson's syndrome and a lifelong risk on experiencing an adrenal crisis.[25] Disadvantages of medical therapy include inefficacy in some patients, development of adverse events and costs. Multiple factors should be considered in the choice of second-line treatment including age, gender, severity of hypercortisolism, need for rapid symptom control, specific co-morbidities, individual features predisposing for development of adverse events, child wish and so forth. (see also section 2). The ultimate decision should be made via a multidisciplinary approach in close consultation with the patient.

NEW DRUG DEVELOPMENTS

Considering the performance of available pituitary-targeting drugs there is an unmet need for corticotroph tumor directed drugs that couple high efficacy to an acceptable side effect profile. In the past decade, cyclin-dependent kinases, the epidermal growth factor receptor (EGFR), histon deactelylases (HDAC) and heat shock protein 90 (HSP90) have been identified as potential targets in corticotroph tumors for medical therapy as demonstrated by in vitro studies with primary corticotroph tumor cells and in vivo studies with experimental animals.[26] This has been translated into a small number of several clinical (pilot) trials with: (a) seliciclib, a cyclin E inhibitor, decreased UFC concentrations without normalization in 9 patients during a 4-w study[27]; (b) gefinitib, a tyrosine kinase inhibitor that inhibits EGFR function, is investigated in a study in CD patients with a tumoral mutation in ubiquitin-specific protease 8 (USP8; NCT02484755). In approximately 50% of corticotroph tumors USP8 mutations are found, which are associated with enhanced-EGFR signaling leading to an increased tumoral ACTH secretion and cell growth.[28,29] Targeting EGFR seems therefore a rational approach, at least in patients with a USP8 mutated adenoma; (c) fimepinostat, a dual inhibitor of HDAC and phosphatidylinositol-3-kinases,[30] is currently investigated in patients with CD (NCT05971758).

Next to receptors and components of various pathways in corticotroph tumors, ACTH and the ACTH receptor may also serve as potential therapeutic targets for medical therapy. A monoclonal antibody against ACTH (ALD1613) counteracting the binding of ACTH to its receptor was shown to decrease corticosterone production in rats in a dose-dependent manner.[31] Currently a multicenter study is investigating the efficacy and safety of the monoclonal ACTH antibody Lu AG13909 in patients with CD (NCT06471829). Another approach is to antagonize the ACTH receptor itself. In a pilot study the nonpeptide selective ACTH antagonist Atumelnant normalized cortisol production within 1 w in 5 patients with ACTH-dependent CS.[32] A multicenter study with Atumelnant in patients with CS has recently been initiated (NCT05804669).

Inhibition of the enzyme 11-beta-hydroxysteroid dehydrogenase type 1 (11-beta-HSD 1) that converts inactive cortisone into active cortisol is a recently developed concept to decrease endogenous cortisol concentrations. The RESCUE study involved a phase II study in which the efficacy of the 11-beta-HSD 1 inhibitor clofutriben was investigated in 17 patients with ACTH-dependent CS.[33] Patients were randomized to 12 w treatment with oral clofutriben 6 mg per day and 12 w of matching placebo in 2 blinded sequences. Clofutriben treatment resulted in a reduction in UFC levels and an improvement of glucose homeostasis and blood pressure regulation. Main side effects were symptoms of steroid withdrawal without occurrence of adrenal insufficiency.

SUMMARY

The choice between different agents is complicated and should be individualized according to various aspects including treatment goals (i.e. normalization of biochemical cortisol excess parameters and its rate, tumor control, etc.),[2,34] drug effectiveness,[35] drug AEs, and tolerability, which can differ between patients[36] and local considerations, such as cost and availability.[37] For various drugs, long-term efficacy and safety data have become available supporting the option of long-term medical therapy in selected cases. There is a significant need of studies addressing unanswered questions and controversies in CD, such as optimal combination treatment,[38–42] role of preoperative and primary medical therapy,[43–45] and treatment of CD during pregnancy.[26] Even in modern times, the negative impact of CD on patients quality of life

and longevity remains significant,[46] but new pharmacologic treatments are under development,[27,32,36] as well as novel imaging modalities enabling better visualization of the corticotroph adenoma,[47,48] might hold careful promise for patients with CD.

CLINICS CARE POINTS

- Long term extension studies have shown good feasibility of medical therapy for long term treatment of Cushing's disease (CD).
- Medical therapy for CD should be chosen according to patient's specific characteristics including among the gender, medical background and personal preferences.
- Close follow up is required during medical therapy for CD due to possible adverse effects as well as the possibility of iatrogenic hypocortisolism.
- Routine reconsideration of medical therapy should be done during patient follow up taking into account new treatment options being developed such as novel imaging modalities, developments in surgical technique and novel medical therapies.

ACKNOWLEDGMENTS

E. Nowak is supported by the Clinician Scientist Program RISE (Rare Important Syndromes in Endocrinology), supported by the Else Kröner-Fresenius-Stiftung and Eva Luise und Horst Köhler Stiftung.

DISCLOSURE

R.A. Feelders has received speaker fees and research grants from Recordati and Corcep, N. Agrawal had a research grant form Recordati. Y. Schwarz, R. Halperin, E. Nowak and S.N. Shah have nothing to declare.

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