Medical Therapy for Cushing Syndrome in the Twenty-first Century

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KEYWORDS

• Cushing syndrome • Cushing disease • Ketoconazole • Metyrapone • Mitotane • Etomidate • Cabergoline • Pasireotide

KEY POINTS

- Medical therapy is useful as adjunct treatment in the management of Cushing syndrome.
- Available medications include steroidogenesis inhibitors, centrally acting agents, and glucocorticoid receptor antagonists.
- The choice between medical treatment options is empiric and requires a careful assessment of risks and benefits of each therapeutic option for an individual patient.
- Several investigational agents are currently under study as potential therapies for Cushing syndrome.
- Novel medical therapies may be developed as a consequence of better understanding of the pathogenesis of the tumors underlying Cushing syndrome.

INTRODUCTION

Prompt control of hypercortisolism is needed to reverse clinical and biochemical manifestations and decrease excess morbidity and mortality in patients with endogenous Cushing syndrome (CS).[1–4] Resection of the underlying tumor is currently the mainstay of treatment of CS.[3] After trans-sphenoidal pituitary surgery, persistent or recurrent hypercortisolism may occur in, respectively, 10% to 20% and 20% to 30% of patients with pituitary corticotroph adenomas (ie, Cushing disease [CD]), which underlies

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approximately 70% of all cases of CS.[3,4] In other patients, the underlying tumor may be difficult to localize or can be unresectable, including in some patients with corticotroph macroadenomas, metastatic neuroendocrine tumors or advanced adrenocortical carcinomas.

The role of medical therapy in CS/CD is currently adjunctive.[3] Medications are often used to control hypercortisolism in patients with CD who have failed trans-sphenoidal pituitary surgery and have received radiation therapy to the sella.[5,6] In these patients, it may take several years for the salutary effects of radiation therapy to develop. In addition, medical therapy may be advised to stabilize the condition of acutely ill patients with CS/CD, who are not fit to undergo definitive surgery immediately. Medical therapy can also be recommended in patients whose surgery has been deferred for various reasons or those whose tumor location is uncertain. Patients with unresectable or metastatic tumors may also benefit from medical therapy to control hypercortisolism. The care of patients with CS/CD generally requires a multimodality approach involving experienced physicians from several disciplines (surgery, neurosurgery, endocrinology, radiation oncology, and medical oncology).

The aims of the present article are to outline current and novel medical therapies for patients with CS/CD. To retrieve pertinent articles, electronic literature searches were conducted using the keyword, CS, CD, medical therapy, treatment, ketoconazole, metyrapone, mitotane, etomidate, cabergoline, pasireotide, and mifepristone. Articles cited in this review were included based on the authors' judgment.

The primary goal of medical therapy is to control hypercortisolism, thereby ameliorating symptoms and signs of CS. Most studies of medical therapies have used 24-hour urine-free cortisol (UFC) as the primary endpoint for efficacy.[3] In addition, some studies have examined the effect of medical therapies on late-night salivary cortisol, a measure of nadir cortisol levels in patients with typical sleep wakefulness cycles, third shift workers thus being excluded.[7] All medications used to treat CS/CD have the potential to decrease cortisol levels and/or mitigate cortisol action below normal, leading to potentially life-threatening hypoadrenalism.[3] Therefore, all patients receiving medical therapy for CS/CD require close follow-up and regular monitoring to establish clinical effectiveness, avert hypoadrenalism, and detect and manage other adverse effects.[5,8]

As shown in **Fig. 1**, medications for CS can be categorized depending on their site of action, including steroidogenesis inhibitors (which inhibit 1 or several enzymes involved in cortisol biosynthesis), centrally acting agents (which interfere with corticotropin release from pituitary corticotroph tumors), and glucocorticoid receptor (GR) antagonists (which inhibit cortisol action).[3] With the exception of pasireotide and mifepristone, agents discussed in this article have not been specifically labeled by the United States Food and Drug Administration (FDA) as therapies for CS/CD. Pasireotide, ketoconazole, and metyrapone are licensed by the European Medicines Agency for CS/CD.

STEROIDOGENESIS INHIBITORS

Steroidogenesis inhibitors in use in CS include ketoconazole, metyrapone, mitotane, and etomidate (**Table 1**).[3] Currently available drugs in this group have been studied in case series but not in controlled clinical trials. Investigational steroidogenesis inhibitors that are in clinical development include osilodrostat (LCI699) (clinicaltrials.gov: NCT02468193 and clinicaltrials.gov: NCT02697734) and levoketoconazole (clinicaltrials.gov: NCT01838551). Steroidogenesis inhibitors have been studied and

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