Medical Treatment of Cushing Disease

New Targets, New Hope

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KEYWORDS

• Cushing disease • Medical therapy • Pasireotide • Mifepristone • LCI699
• Combination therapies

KEY POINTS

- For most patients with Cushing disease, transsphenoidal surgery remains the first-line therapy of choice; however, many patients will not achieve remission or will experience tumor recurrence.
- Pasireotide may be an attractive option as an initial medical therapy for some patients. Hyperglycemia is frequent but rarely severe; intense monitoring and timely treatment are required.
- Mifepristone may be appropriate in patients with diabetes mellitus, whereas patients with severe hypertension and uncontrolled hypokalemia are not good candidates.
- Several adrenal steroidogenesis inhibitors continue to be used off-label, with varying results.
- The value of medical combination therapy is still under investigation, and new medical therapies are in development.

INTRODUCTION

Cushing disease (CD) is a condition of hypercortisolism caused by a corticotropin (adrenocorticotropic hormone [ACTH])-secreting pituitary adenoma. If untreated, CD is associated with significant morbidity and mortality[1–3]; however, some investigators have suggested that early and aggressive intervention can increase survival.[2,3]

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Successful patient management requires individualized and multidisciplinary care involving endocrinologists, neurosurgeons, radiation oncologists, and general surgeons (**Box 1**).[1,4,5]

For most CD patients, transsphenoidal surgery remains the first-line therapy of choice.[6] Other treatment modalities include medication, radiation therapy, and bilateral adrenalectomy.[1,6–8]

This article focuses on the most recent medical therapeutic advances, in particular newly approved ACTH modulators, a glucocorticoid receptor blocker, and a novel adrenal steroidogenesis inhibitor; other drugs are also discussed (**Table 1**).[1,6,7,9–15]

PITUITARY TARGETED MEDICAL THERAPY

Medications that exert effects at the level of the pituitary represent an appealing option for CD treatment.[16–19]

Somatostatin receptor ligands (SRLs) and dopamine agonists (DAs) that target corticotroph adenomas, which predominantly express somatostatin receptor (Sstr) subtype 5 and DA2 receptors, currently represent the 2 main classes of centrally acting drugs used to treat CD.

Somatostatin Receptor Ligand: Pasireotide (SOM230; Signifor)

Pasireotide (Novartis Pharmaceuticals, Basel Switzerland) is a cyclic hexapeptide with a high affinity for Sstrs 1, 2, 3, and 5[19–22]; affinity for Sstr 5 is 40-fold higher than other first-generation SRLs.[22]

Pasireotide reduces ACTH secretion in cell culture models and in cultured human corticotroph tumor cells.[23] In phase II and III studies, pasireotide was found to be efficacious in treating CD, although some limitations and adverse effects were recognized.

In a phase II, proof-of-concept, open-label, single-arm, 15-day multicenter study, pasireotide decreased urine free cortisol (UFC) levels in 76% of CD patients with direct effects on ACTH release. Hyperglycemia occurred in 36% of patients, some with pretreatment glucose abnormalities. Steady-state plasma pasireotide concentrations were achieved within 5 days of treatment. Intriguingly, responders appeared to have higher pasireotide exposure than nonresponders (**Box 2**).[8,21]

In a long-term extension to this study, the reductions in mean UFC persisted in all patients who were still taking the study drug at 2 years, albeit with an inherent selection bias for patients who continued in extension.[20]

Box 1
Therapy options in clinical practice

- Transsphenoidal surgery is the treatment of choice for most patients with Cushing disease
- If surgery fails, or the disease recurs, there are several possible treatment alternatives:
  - Medical therapy
  - Repeat surgery
  - Radiation and medical therapy
  - Bilateral adrenalectomy
- Lifelong monitoring for possible recurrence is required