New developments in the medical treatment of Cushing’s syndrome

R van der Pas, W W de Herder, L J Hofland and R A Feelders

Division of Endocrinology, Department of Internal Medicine, Erasmus Medical Center, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands

(Correspondence should be addressed to R A Feelders; Email: r.feelders@erasmusmc.nl)

Abstract

Cushing’s syndrome (CS) is a severe endocrine disorder characterized by chronic cortisol excess due to an ACTH-secreting pituitary adenoma, ectopic ACTH production, or a cortisol-producing adrenal neoplasia. Regardless of the underlying cause, untreated CS is associated with considerable morbidity and mortality. Surgery is the primary therapy for all causes of CS, but surgical failure and ineligibility of the patient to undergo surgery necessitate alternative treatment modalities. The role of medical therapy in CS has been limited because of lack of efficacy or intolerability. In recent years, however, new targets for medical therapy have been identified, both at the level of the pituitary gland (e.g. somatostatin, dopamine, and epidermal growth factor receptors) and the adrenal gland (ectopically expressed receptors in ACTH-independent macronodular adrenal hyperplasia). In this review, results of preclinical and clinical studies with drugs that exert their action through these molecular targets, as well as already established medical treatment options, will be discussed.

Introduction

Cushing’s syndrome (CS) is characterized by chronic overproduction of cortisol resulting in significant morbidity and, when untreated, an increased mortality (Lindholm et al. 2001, Newell-Price et al. 2006, Dekkers et al. 2007, Clayton et al. 2011, Hassan-Smith et al. 2012). Traditionally, CS is divided into ACTH-dependent CS and ACTH-independent CS. ACTH-dependent CS, ~80% of cases, can be caused by a corticotroph pituitary adenoma and, more rarely, by ectopic ACTH production. ACTH-independent CS is usually caused by a unilateral adrenal adenoma and less frequently by an adrenal carcinoma or bilateral micro- or macronodular adrenal hyperplasia (Boscaro et al. 2001, Newell-Price et al. 2006).

Chronic cortisol excess leads to a typical clinical phenotype with truncal and facial fat deposition, plethoric facial appearance, easy bruisability, and muscle and skin atrophy (Table 1), although the prevalence of these symptoms can be highly variable and in part related to the underlying cause of CS (Newell-Price et al. 2006, Nieman et al. 2008). In addition, chronic hypercortisolism is associated with serious morbidity including an increased cardiovascular risk due to clustering of risk factors (obesity, diabetes mellitus, hypertension, and dyslipidemia); an increased risk of venous thromboembolism, osteoporosis, and psychological and cognitive disturbances (Newell-Price et al. 2006, Pereira et al. 2010, Stuijver et al. 2011). This multitude of signs, symptoms, and morbidity severely impairs quality of life in patients with CS (Johnson et al. 2003, Webb et al. 2008). If CS is not or suboptimally treated, continuous cortisol excess will lead to an increased mortality in particular due to cardiovascular disease (Plotz et al. 1952, Lindholm et al. 2001, Dekkers et al. 2007, Clayton et al. 2011, Hassan-Smith et al. 2012). Several diagnostic tests are used to establish endogenous hypercortisolism including urinary free cortisol (UFC) excretion, dexamethasone suppression test(s), and midnight serum or salivary cortisol levels (Nieman et al. 2008).

The first-line treatment of all forms of CS is surgery. However, additional treatment modalities are necessary when surgery is not successful (e.g. in pituitary-dependent CS), not indicated (e.g. in case of metastatic disease), or in case of high surgical risk (e.g. in patients with severe co-morbidity). These therapeutic options
Table 1 Clinical features observed in Cushing’s syndrome

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>39–96</td>
</tr>
<tr>
<td>Facial plethora</td>
<td>82–90</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>24–90</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>60–82</td>
</tr>
<tr>
<td>Menstrual irregularity</td>
<td>74–80</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>50–80</td>
</tr>
<tr>
<td>Hypertension</td>
<td>62–78</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>72–75</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>38–75</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>53–70</td>
</tr>
<tr>
<td>Easy bruising</td>
<td>46–65</td>
</tr>
</tbody>
</table>


include radiotherapy, bilateral adrenalectomy, and medical therapy. Each of these options has its limitations due to variable response rates and complications, and in each individual patient, the pros and cons of each second-line treatment modality should be carefully weighed. In the past decades, the role of medical therapy for CS was limited due to lack of efficacy and/or safety issues. However, in recent years, new targets for medical treatment have been identified. Translational research and subsequent clinical studies have opened new perspectives for medical treatment. In this review, we will discuss the currently available drugs to treat CS and focus on new developments in medical therapy for CS in the context of various treatment aims for different causes of CS.

CS etiology, clinical features, and therapeutic approach

ACTH-dependent CS

Pituitary-dependent CS

Pituitary-dependent CS or Cushing’s disease (CD) is caused by an ACTH-secreting pituitary adenoma and accounts for ~70% of all cases of endogenous CS (Boscaro et al. 2001, Newell-Price et al. 2006, Biller et al. 2008, Bertagna et al. 2009). Clinical symptoms develop gradually, which often delays the diagnosis for years. The primary treatment of CD is a transsphenoidal resection of the adenoma. Long-term remission rates after surgery vary between 50 and 90% (Atkinson et al. 2005, Biller et al. 2008, Tritos et al. 2011), but a recurrence risk of up to 26% has been observed during 10 years of follow-up (Atkinson et al. 2005, Tritos et al. 2011). The outcome of surgery is highly dependent on the size of the adenoma, as macroadenomas and non-visible adenomas have a relatively poor success rate compared with microadenomas (Rees et al. 2002, Mullan & Atkinson 2008). As repeat pituitary surgery has a relatively disappointing success rate and is often complicated by hypopituitarism, there is a clear need for alternative treatment modalities (Ram et al. 1994, Esposito et al. 2006, Biller et al. 2008). In cases of disease recurrence or persistent hypercortisolism after surgery, radiotherapy can be applied to induce definitive remission. However, it can take years for radiotherapy to become effective, leaving the patients exposed to the toxic effects of cortisol excess. In addition, 30–40% of patients develop pituitary insufficiency after pituitary irradiation (Boscaro et al. 2001, Devin et al. 2004, Vance 2005, Biller et al. 2008, Petit et al. 2008, Bertagna et al. 2009, Tritos et al. 2011). Medical treatment for patients with persistent or recurrent CD has the advantage over radiotherapy of a direct onset of action and preserving pituitary function. Medical treatment options for CD are discussed in ‘Medical treatment modalities’ and ‘Medical therapy for different causes of CS’ sections.

Ectopic ACTH syndrome

The ectopic ACTH syndrome (EAS) causes ~10% of all cases of CS (Ilias et al. 2005, Newell-Price et al. 2006, Tritos et al. 2011). EAS is predominantly caused by neuroendocrine tumors (e.g. bronchial, thymic, or pancreatic neuroendocrine tumors), but small-cell lung carcinomas, pheochromocytomas, medullary thyroid carcinomas, and neuroendocrine prostate carcinomas are also possible sources of ectopic ACTH production (Aniszewski et al. 2001, Ilias et al. 2005, Isidori et al. 2006, Biller et al. 2008). CS caused by bronchial carcinoids can mimic CD with a gradual development of symptoms, but florid CS usually develops much faster in EAS. Because ACTH and cortisol levels are often higher in patients with EAS than in CD, symptoms like hyperpigmentation of the skin (due to excessive pro-opiomelanocortin (POMC)/α-MSH production) and mineralocorticoid effects (due to overwhelming cortisol levels exceeding renal 11β-hydroxysteroid dehydrogenase type II capacity) like hypertension, hypokalemia, and edema predominate in EAS as presenting symptoms rather than the typical
clinical phenotype (Table 2: Ilias et al. 2005, Isidori et al. 2006). When possible, surgery is the primary treatment option for EAS. Reported success rates of curative surgery vary from 12 to 83%, depending on the cause of EAS (Aniszewski et al. 2001, Ilias et al. 2005, Isidori et al. 2006). In case of metastatic disease, alternative treatment options include radiotherapy, radio frequency ablation, systemic chemotherapy, bilateral adrenalectomy, and medical therapy to decrease ACTH or cortisol production. Patients with occult ACTH-secreting tumors can be treated with bilateral adrenalectomy or medical therapy (Aniszewski et al. 2005). Medical treatment options for EAS are discussed in ‘Medical treatment modalities’ and ‘Medical therapy for different causes of CS’ sections.

**ACTH-independent CS**

ACTH-independent CS accounts for 20% of all causes of CS and is most frequently caused by a unilateral cortisol-producing adenoma and more rarely by bilateral micro- or macronodular adrenal hyperplasia (AIMAH) and a cortisol-producing adrenal carcinoma.

**Adrenal adenoma and bilateral adrenal hyperplasia**

Cortisol-producing adrenal adenoma and AIMAH can occur sporadically but also as part of a genetic syndrome like multiple endocrine neoplasia syndrome type 1, the McCune–Albright syndrome (somatic mutation in the \( \alpha \)-subunit of the G-protein resulting in constitutive activation of the cAMP pathway), and Carney complex (due to PRKAR1A mutation; Yaneva et al. 2010). Apart from a clinically evident CS with established hypercortisolism, adrenal adenomas and AIMAH can also be associated with the so-called subclinical CS (Chiodini 2011).

In AIMAH and to a lesser extent in unilateral adenomas, cortisol production can be regulated by ectopic stimuli. Based on ectopic hormone receptor expression or increased eutopic hormone receptor expression on adrenocortical cells, stimuli other than ACTH can regulate cortisol production via abnormal coupling between the involved receptor and steroidogenesis (Lacroix 2009). Ectopic/eutopic receptors associated with AIMAH and cortisol-producing adenoma include those for glucose-dependent insulinotropic peptide (GIP), vasopressin, TSH, serotonin, LH, and catecholamines. The presence of these receptors can be demonstrated by aberrant cortisol responses to administrated stimuli (e.g. vasopressin, LHRH, and TRH; Lacroix 2009).

Cortisol-producing adrenal adenomas are usually small and can surgically be removed by laparoscopic adrenalectomy. AIMAH is primarily treated surgically as well, by bilateral adrenalectomy. Tumors larger than 6 cm are usually treated by an open adrenalectomy, in particular when adrenal carcinoma is suspected based on the imaging phenotype (Cuesta et al. 1996). Identification of ectopic hormone receptor expression may offer perspectives for medical treatment with drugs that block the involved receptor or that inhibit production of the endogenous ligand (see ‘Medical therapy for different causes of Cushing’s syndrome–ACTH-independent CS’ section below). The optimal management of subclinical CS has not been established yet (Chiodini 2011).

**Adrenocortical carcinoma**

Hormonal overproduction occurs in about 60% of adrenocortical carcinomas (ACCs), and the majority of these tumors secrete cortisol whether or not in combination with androgens (Wajchenberg et al. 2000). Patients with hormonal overproduction can present with CS and/or virilization. ACC are usually large tumors and surgical resection is the only curative treatment option. In patients with (limited) metastasized disease, surgical debulking can be considered, in combination with medical therapy (see ‘Medical treatment modalities–Inhibitors of adrenocortical steroidogenesis and Medical therapy for different causes of Cushing’s syndrome–ACTH-independent CS’ section below), to decrease hormone excess. After resection of an ACC, there is a considerable recurrence risk, in particular in case of large tumors. Adjuvant treatment...
Indications for medical therapy

There are several treatment aims for medical therapy in CS (Table 3; Morris & Grossman 2002, Feelders et al. 2010c). Medical treatment can be indicated because of acute complications of CS like acute psychosis, severe hypertension, and opportunistic infections. These potentially life-threatening conditions are mainly associated with the EAS (see ‘ACTH-dependent CS–Ectopic ACTH syndrome’ section below) and require rapid reversal of cortisol excess. Furthermore, cortisol-lowering medical therapy is given in some centers as pretreatment before pituitary surgery with the aim to optimize a patient’s condition, i.e. to decrease catabolism and improve regulation of blood pressure and glucose homeostasis, in order to reduce perioperative morbidity. In addition, lowering cortisol production may decrease bleeding tendency in the surgical area. Although this may be a rationale concept, no studies have been performed that prove efficacy of preoperative medical treatment (Feelders et al. 2010c). A large retrospective cohort study showed that, compared to treatment-naïve patients, patients that are treated with cortisol-lowering therapy before surgery seem to have a reduced risk for developing venous thromboembolism postoperatively, although this difference was not statistically significant (Stuijver et al. 2011). Medical therapy can further be considered in patients with CD with a low a priori chance on surgical cure, i.e. in case of an adenoma with an unfavorable localization, e.g. in the parasellar region. The chances on cure in patients with invisible adenomas are also lower, although surgery can still be successful. Finally, medical therapy is indicated for treatment of hypercortisolism: 1) after unsuccessful surgery for pituitary-dependent CS or the EAS; 2) in patients with metastasized disease, i.e. ACTH-producing neuroendocrine tumors and cortisol-producing ACC; and 3) in patients with any cause of CS with a high operation risk due to, e.g. co-morbidities or high age. Quantitatively, patients with persistent or recurrent pituitary-dependent CS represent the largest group that needs medical therapy to control hypercortisolism. As outlined in the ‘Pituitary-dependent CS’ section above, pituitary surgery is not successful in 10–50% of patients (Atkinson et al. 2005, Biller et al. 2008, Tritos et al. 2011) and recurrences occur in up to 26% of patients (Atkinson et al. 2005, Tritos et al. 2011). In these patients, it is essential to induce long-term normalization of cortisol production in order to reverse co-morbidity, improve quality of life, and normalize life expectancy (Biller et al. 2008). For this purpose, medical therapy can be applied either as chronic treatment or as bridging therapy during the period after which radiotherapy becomes effective.

Medical treatment modalities

This paragraph gives a brief overview of available drugs and their biochemical targets for treatment of CS (Table 4). Details on dosages and combination therapy are described in ‘Medical therapy for different causes of CS’ section.

Pituitary-targeted drugs

Drugs with proven clinical efficacy

In recent years, dopamine receptors and somatostatin receptors have been identified as therapeutic targets on corticotroph adenomas (de Bruin et al. 2009b). Approximately 80% of ACTH-secreting pituitary adenomas express the dopamine receptor subtype 2 (D2R; Pivonello et al. 2004, de Bruin et al. 2009b). Cabergoline is an ergot-derived dopamine agonist with particular high affinity for the D2R. Both in vitro and in vivo studies showed that cabergoline was efficacious with respect to inhibition of ACTH and cortisol secretion (discussed the ‘Medical therapy for different causes of CS–Pituitary-dependent CS’ section below). In an in vitro setting, Pivonello et al. (2004) found that dopamine agonist treatment with either bromocriptine or cabergoline inhibited ACTH secretion in 100% of D2R-positive adenomas. Frequently occurring but mostly transient side effects of cabergoline include nausea, headache, dizziness, and abdominal discomfort (Pivonello et al. 2009, Godbout et al. 2010). A point of concern, although controversial, is the possible association between chronic use of cabergoline and the development of valvular heart disease. In different studies in which patients with CD were treated with

Table 3 Possible indications for medical therapy of Cushing’s syndrome

| Acute complications of (severe) hypercortisolism |
| Pretreatment before pituitary surgery |
| After unsuccessful surgery |
| Bridging therapy after pituitary irradiation |
| Primary medical therapy in Cushing’s disease |
| Adenoma with unfavorable localization |
| Invisible adenomas (?) |
| Inoperability |
| Metastatic disease |
| High operation risk |
cabergoline, dosages varying from 0.5 up to 7 mg/week were used (Pivonello et al. 2009, Godbout et al. 2010, Vilar et al. 2010). Patients with Parkinson’s disease are treated with much higher dosages of cabergoline, which can cause cardiac valve fibrosis via serotonin receptor 2B-mediated activation of valvular fibroblasts (Schade et al. 2007, Zanettini et al. 2007). In cabergoline-treated patients with prolactinomas, an increased prevalence of valvular calcification was found, but this was not accompanied by valvular dysfunction (Delgado et al. 2011).

To date, five somatostatin receptor subtypes (sst) have been identified (Patel 1999). Corticotroph pituitary adenomas predominantly express the sst5 (de Bruin et al. 2009b). In contrast to GH-producing pituitary adenomas, which have a high degree of sst2 expression, sst2 expression by corticotroph adenomas is low (de Bruin et al. 2009a).

This explains why the sst2-targeting somatostatin analogs octreotide and lanreotide are generally ineffective in the treatment of CD (Lamberts et al. 1989, Stalla et al. 1994). The low sst2 expression is thought to result from downregulating effects of high circulating cortisol levels. Indeed, several in vitro studies suggested that exposure to glucocorticoids diminishes sst2 expression both in GH- and ACTH-secreting cell lines (Schonbrunn 1982, Stalla et al. 1994, Xu et al. 1995, Park et al. 2003, de Bruin et al. 2009a).

Pasireotide is a somatostatin analog, which binds sst1, 2, 3, 5 with high affinity (Bruns et al. 2002). In particular, it has subnanomolar affinity for the sst5, the predominant sst in corticotroph pituitary adenomas (Bruns et al. 2002, Hofland et al. 2005). Early in vitro studies performed by Hofland et al. showed that pasireotide (10 nmol/l) significantly inhibited ACTH secretion by 30–40% in 3/5 primary cultures of human corticotroph pituitary adenomas. Three clinical studies have shown that pasireotide in dosages between 750 and 2400 mg/day can reduce UFC levels in patients with CD (see the ‘Medical therapy for different causes of CS–Pituitary-dependent CS’ section below). Induction of hyperglycemia, which may require glucose-lowering therapy, is an important side effect of pasireotide (Boscaro et al. 2009, Feelders et al. 2010a,b, Colao et al. 2012). In healthy volunteers, pasireotide-induced hyperglycemia was shown to be due to inhibition of incretin secretion with a concomitant decreased insulin secretion (Henry et al. 2011). Glucose levels were most effectively lowered with glucagon-like peptide 1 agonists or dipeptidyl peptidase 4 (an enzyme that inactivates the incretins) inhibitors (Henry et al. 2011). Other than hyperglycemia, pasireotide might cause gastrointestinal side effects (Boscaro et al. 2009, Colao et al. 2012).

Finally, the alkylating chemotherapeutic drug temozolomide, which is used to treat malignant brain tumors, has been reported to be of value in case of aggressive corticotroph pituitary adenomas that are refractory to surgery or pituitary irradiation (Mohammed et al. 2009, Curto et al. 2010, Raverot et al. 2010, Dillard et al. 2011, McCormack et al. 2011).

### Table 4 Dosages and most important side effects of drugs used to treat Cushing’s syndrome

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
<th>Dosage</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary-targeted drugs</td>
<td>Cabergoline</td>
<td>Up to 7 mg/week</td>
<td>Headache, dizziness, gastrointestinal discomfort, and cardiac valve fibrosis</td>
</tr>
<tr>
<td>Inhibitors of adrenocortical</td>
<td>Pasireotide</td>
<td>750–2400 µg/day</td>
<td>Hyperglycemia, GH deficiency, and gastrointestinal discomfort</td>
</tr>
<tr>
<td>steroidogenesis</td>
<td>Ketoconazole</td>
<td>400–1600 mg/day</td>
<td>Hepatotoxicity, gynecomastia, and gastrointestinal discomfort</td>
</tr>
<tr>
<td></td>
<td>Metyrapone</td>
<td>0.5–4.5 g/day</td>
<td>Dizziness, rash, gastrointestinal discomfort, worsening of hypertension, acne, and hirsutism</td>
</tr>
<tr>
<td></td>
<td>Mitotane</td>
<td>3–5 g/day</td>
<td>Gynecomastia, hepatotoxicity, hypercholesterolemia, prolonged bleeding time, gastrointestinal discomfort, dizziness, ataxia, confusion, dysarthria, and memory problems</td>
</tr>
<tr>
<td>Glucocorticoid receptor antagonists</td>
<td>Etomidate</td>
<td>0.1–0.3 mg/kg per h</td>
<td>Nephrotoxicity</td>
</tr>
<tr>
<td></td>
<td>Mifepristone</td>
<td>300–1200 mg/day</td>
<td>Hypokalemia, worsening of hypertension, clinical adrenal insufficiency, endometrial hyperplasia, and gastrointestinal discomfort</td>
</tr>
</tbody>
</table>

Mary A. McCormack and Renata R. Auge de Castilho

Endocrine-Related Cancer (2012) 19 R205–R223
Drugs with promising in vitro results
Retinoic acid has been shown to inhibit POMC transcription and ACTH secretion both in the murine AtT20 cell-line and in the primary cultures of human corticotroph pituitary adenoma cells (Paez-Pereda et al. 2001). In addition, this study showed that retinoic acid inhibited AtT20 cell proliferation by inducing apoptosis. Finally, both pretreatment of AtT20 cells with retinoic acid before injection and treating retinoic acid-naïve AtT20 tumor cells resulted in inhibition of AtT20 tumor formation in nude mice inoculated with these AtT20 cells (Paez-Pereda et al. 2001).

A subsequent study performed by the same group showed that, without inducing toxicity, retinoic acid decreased urinary cortisol/creatinine ratios, plasma ACTH, and pituitary adenoma size in dogs with CD (Castillo et al. 2001). In addition, this study showed that retinoic acid inhibited tumor growth by 40% compared with vehicle-treated animals. Serum corticosterone levels were also decreased by gefitinib, which was accompanied by improvement of clinical signs, e.g. fat accumulation, hyperglycemia, and weight gain (Fukuoka et al. 2011). Although not yet evaluated in humans, the EGFR may be a promising target.

In addition to D2R and sst5, corticotroph pituitary adenomas have been shown to express peroxisome proliferator-activated receptor γ (PPARγ). Although initial studies showed that high dosages of the thiazolidinediones were able to inhibit tumor growth and ACTH and corticosterone levels in mice (Heaney et al. 2002), the results of thiazolidinedione treatment in patients with CD and Nelson’s syndrome (NS) have been rather disappointing (Ambrosi et al. 2004, Suri & Weiss 2005, Mullan et al. 2006, Pecori Giraldi et al. 2006, Munir et al. 2007, Kreutzer et al. 2009). Therefore, PPARγ agonists do not play a role in the medical treatment of CD.

Although serotonin receptor antagonists and vasopressin receptor antagonists were initially believed to decrease ACTH secretion in patients with CD, they have not proven their clinical efficacy and are therefore not recommended in the treatment of CD (Biller et al. 2008).

Inhibitors of adrenocortical steroidogenesis
Ketoconazole is an imidazole derivative that was originally developed to treat fungal infections. However, ketoconazole has also been shown to inhibit adrenocortical steroidogenesis when administered in high dosages, i.e. between 400 and 1600 mg/day (Castinetti et al. 2008). Its main mechanism of action is inhibition of the steroidalogenic enzymes 17-hydroxylase and 17,20-lyase and it is one of the most frequently used cortisol-lowering drugs (Engelhardt et al. 1985, Loli et al. 1986, Lamberts et al. 1987, McCance et al. 1987, Sonino 1987, Farwell et al. 1988, Sonino et al. 1991, Biller et al. 2008, Castinetti et al. 2008). Ketoconazole is hepatotoxic, can cause gynecomastia, and has serious, mainly gastrointestinal, side effects, which together can limit its long-term use (McCance et al. 1987, Sonino et al. 1991, Como & Dismukes 1994, Nieman 2002, Castinetti et al. 2008). Ketoconazole may also have inhibitory effects on ACTH secretion by corticotroph tumor cells (Stalla et al. 1988, Feelders et al. 2010c). This might explain the absence of a rise in ACTH levels during ketoconazole treatment in response to a decrease in cortisol levels. Although an increase in ACTH production upon ketoconazole treatment was found in rats (Burrin et al. 1986), several studies show no rise in ACTH concentrations in patients with CD following treatment with ketoconazole (Loli et al. 1986, Terzolo et al. 1988, Sonino et al. 1991). In recent clinical trials, ketoconazole has been combined with either pituitary-targeted medical therapy or other adrenal-blocking drugs (Feelders et al. 2010a,b, Vilar et al. 2010, Kamenicky et al. 2011). Combination therapy for CS will be discussed in ‘Medical therapy for different causes of CS’ section.

Metyrapone is another frequently used inhibitor of steroidogenesis. Its main site of action is 11β-hydroxylase, as Verhelst et al. (1991) found a concomitant decrease in cortisol concentrations and increase in 11-deoxycortisol levels in 91 CS patients treated with metyrapone. Side effects that occur during metyrapone therapy include dizziness, rash, and gastrointestinal complaints (Tritos et al. 2011). In addition, concentrations of mineralocorticoid precursors and adrenal androgens can increase due to

Inhibitors of adrenocortical steroidogenesis
Ketoconazole is an imidazole derivative that was originally developed to treat fungal infections. However, ketoconazole has also been shown to inhibit adrenocortical steroidogenesis when administered in high dosages, i.e. between 400 and 1600 mg/day (Castinetti et al. 2008). Its main mechanism of action is inhibition of the steroidalogenic enzymes 17-hydroxylase and 17,20-lyase and it is one of the most frequently used cortisol-lowering drugs (Engelhardt et al. 1985, Loli et al. 1986, Lamberts et al. 1987, McCance et al. 1987, Sonino 1987, Farwell et al. 1988, Sonino et al. 1991, Biller et al. 2008, Castinetti et al. 2008). Ketoconazole is hepatotoxic, can cause gynecomastia, and has serious, mainly gastrointestinal, side effects, which together can limit its long-term use (McCance et al. 1987, Sonino et al. 1991, Como & Dismukes 1994, Nieman 2002, Castinetti et al. 2008). Ketoconazole may also have inhibitory effects on ACTH secretion by corticotroph tumor cells (Stalla et al. 1988, Feelders et al. 2010c). This might explain the absence of a rise in ACTH levels during ketoconazole treatment in response to a decrease in cortisol levels. Although an increase in ACTH production upon ketoconazole treatment was found in rats (Burrin et al. 1986), several studies show no rise in ACTH concentrations in patients with CD following treatment with ketoconazole (Loli et al. 1986, Terzolo et al. 1988, Sonino et al. 1991). In recent clinical trials, ketoconazole has been combined with either pituitary-targeted medical therapy or other adrenal-blocking drugs (Feelders et al. 2010a,b, Vilar et al. 2010, Kamenicky et al. 2011). Combination therapy for CS will be discussed in ‘Medical therapy for different causes of CS’ section.

Metyrapone is another frequently used inhibitor of steroidogenesis. Its main site of action is 11β-hydroxylase, as Verhelst et al. (1991) found a concomitant decrease in cortisol concentrations and increase in 11-deoxycortisol levels in 91 CS patients treated with metyrapone. Side effects that occur during metyrapone therapy include dizziness, rash, and gastrointestinal complaints (Tritos et al. 2011). In addition, concentrations of mineralocorticoid precursors and adrenal androgens can increase due to
the 11β-hydroxylase block and the subsequent increase in ACTH production, which stimulates steroidogenesis (Nieman 2002, Tritos et al. 2011). As a result, metyrapone administration might be accompanied by worsening of hypertension, acne, and hirsutism (Verhelst et al. 1991, Nieman 2002, Feelders et al. 2010c). In contrast to ketoconazole, metyrapone does not cause gynecomastia. Hence, metyrapone might preferably be used in males, whereas ketoconazole may be more appropriate to treat female patients with CS (Stewart & Petersenn 2009). However, although metyrapone treatment often has a good short-term response, long-term efficacy data are scarce. Metyrapone treatment often has a good short-term CS (Stewart & Petersenn 2009). However, although metyrapone treatment often has a good short-term response, long-term efficacy data are scarce. Metyrapone is not commercially available in the US. Similar to ketoconazole, metyrapone has been used in combination with other pituitary- or adrenocortical-targeted drugs (Thoren et al. 1985, Kamenicky et al. 2011). Studies addressing combination therapy will be further detailed in ‘Medical therapy for different causes of CS’ section.

Mitotane or o,p’-DDD is a derivative of DDT (dichlorodiphenyltrichloroethane) and is mainly used in the treatment of ACCs because of its adrenolytic properties (Veytsman et al. 2009, Fassnacht et al. 2011). It has been shown to inhibit cortisol production via inhibition of multiple steroidogenic enzymes and to be efficacious in the treatment of CD (Young et al. 1973, Luton et al. 1979). Mitotane has a slow onset of action and based on its lipophilic nature, it is stored in adipose tissue, ensuring a long half-life of 18–159 days (Nieman 2002). Consequently, mitotane remains present in the body, even up to 2 years after withdrawing the drug (Nieman 2002, Tritos et al. 2011). Especially when administered in high dosages, mitotane has many side effects including gastrointestinal (anorexia, nausea, vomiting, and diarrhea) and neurological (dizziness, ataxia, confusion, dysarthria, and memory problems) complaints (Nieman 2002, Fassnacht & Alloio 2009, Schteingart 2009) that require close monitoring of the patient and plasma mitotane concentrations. Other frequently reported adverse events are gynecomastia, hepatotoxicity, hypercholesterolemia, and prolonged bleeding time. Owing to its adrenolytic nature, mitotane often causes adrenal insufficiency necessitating concomitant hydrocortisone substitution (Fassnacht & Alloio 2009).

Similar to ketoconazole, etomidate is an imidazole derivative (Alloio et al. 1983). Originally used as an anesthetic agent, etomidate, which is administered i.v., was soon reported to cause adrenocortical insufficiency in critically ill patients (Fellows et al. 1983). Subsequent studies showed that etomidate can be used to induce eucortisolemia in patients with CS (Schulte et al. 1990, Krakoff et al. 2001). Its suggested mechanism of action is inhibition of the 11β-hydroxylase and cholesterol side-chain cleavage enzymes (Lamberts et al. 1987, Schteingart 2009). Currently, etomidate infusion is used to obtain rapid control of hypercortisolism in severe cases of CS (e.g. in case of glucocorticoid-induced psychosis), in which oral cortisol-lowering agents are ineffective or oral therapy is impossible (Biller et al. 2008).

Aminoglutethimide was first reported to successfully reduce cortisol levels in patients with functional ACCs (Schteingart et al. 1966). The same group reported that, due to increased ACTH levels overriding the cortisol-lowering effect, aminoglutethimide only had temporary suppressive effects in patients with ACTH-dependent CS (Schteingart & Conn 1967). Since 2007, aminoglutethimide is no longer available (Schteingart 2009).

LCI699, a novel inhibitor of 11β-hydroxylase, has been introduced very recently. The efficacy of this agent has been assessed in a small number of patients with CD (Bertagna et al. 2012). Like other adrenal-targeted drugs, this novel compound obviously does not target the cause of the disease in these patients. The clinical applicability and optimal dosage of LCI699 have to be further elucidated.

**Glucocorticoid receptor antagonists**

Mifepristone is the only glucocorticoid receptor (GR) antagonist that is currently available (Castinetti et al. 2009) and counteracts the effect of cortisol at tissue level. It was initially developed as a compound with antiprogestin activity by blocking the progestin receptor. Subsequently, antiglucocorticoid effects were recognized because mifepristone binds to the GR with an 18-fold higher affinity than cortisol (Fleseriu et al. 2012). As a consequence, cortisol cannot exert its negative feedback effects at the hypothalamic and pituitary level, which can lead to an increase in ACTH secretion with a concomitant increased cortisol production. A disadvantage of mifepristone is that there is no biochemical parameter available according to which the mifepristone dose can be adjusted. Consequently, clinical adrenal insufficiency can develop after overtreatment, which may require dose interruption and corticosteroid replacement. In female patients, mifepristone can cause endometrial hyperplasia, which requires ultrasonic monitoring. In addition, increasing cortisol levels during mifepristone treatment can cause mineralocorticoid effects with induction or worsening of hypokalemia and hypertension (Castinetti et al. 2009, Tritos et al. 2011,
Fleseriu et al. 2012). Theoretically, long-term use of mifepristone could provoke NS in patients with CD. Dose titration of mifepristone should be performed according to clinical signs and serum potassium levels (Castinetti et al. 2009).

Medical therapy for different causes of CS

Pituitary-dependent CS

Optimal medical therapy for CD would normalize ACTH and cortisol production without escape, stabilize, or reduce tumor growth; reverse morbidity and mortality; and improve quality of life (Biller et al. 2008). Unfortunately, to date, no long-term efficacy and safety data are available of any available drug.

As already described in ‘Pituitary-targeted drugs’ section, ACTH-secreting pituitary adenomas predominantly express D2R and sst5, which can serve as targets for medical therapy (Pivonello et al. 2004, de Bruin et al. 2009b). Recently, three studies were published in which the effects of cabergoline monotherapy in patients with CD were evaluated (Pivonello et al. 2009, Godbout et al. 2010, Vilar et al. 2010). The first study was performed in 20 patients with persistent CD after surgery. After 3 months of treatment, ACTH concentrations had decreased by more than 25% in 15 of these patients. After 2 years of treatment, 7/20 patients had escaped from cabergoline therapy and 8/20 (40%) were in sustained remission with a median cabergoline dosage of 3.5 mg/week (Pivonello et al. 2009). A retrospective analysis of 30 patients treated with cabergoline monotherapy showed a 50% response rate (either complete or partial) after 6 months of treatment with cabergoline in a mean dose of 1.5 mg/week (Godbout et al. 2010). Long-term analysis showed a sustained normalization of UFC excretion in 9/30 (30%) patients after a mean of 37 months treated with, on average, 2.1 mg/week (range 0.5–6 mg/week). However, in the group of non-responders, the mean cabergoline dose was only 2 mg/week (range 1–4.5 mg/week) for an average period of 4 months (range 1–9 months). The relatively low dose of cabergoline that was used in most patients in this study might have underestimated the maximal inhibitory effect (Godbout et al. 2010). Another recently published study prospectively evaluated the effects of low-dose cabergoline (up to 3 mg/week) in 12 patients with persistent CD after unsuccessful surgery. After 6 months, UFC excretion had normalized in three patients (25%; Vilar et al. 2010). In the other patients, cabergoline decreased UFC excretion by 15–48%. Again, the modest cabergoline dosage might have caused underestimation of the maximal inhibitory effect (Vilar et al. 2010). In this study, low-dose ketoconazole (200–400 mg daily) was added to cabergoline in case of persistent hypercortisolism after 6 months of cabergoline monotherapy. Interestingly, UFC excretion normalized in 6/9 patients with cabergoline and low-dose ketoconazole combination therapy after an additional 6 months of treatment (Vilar et al. 2010).

The efficacy of pasireotide, which targets the sst5, in a clinical setting was first evaluated by Boscaro et al. (2009). In this study, 29 patients with pituitary-dependent CS were treated with pasireotide 600 mg s.c. twice daily during 15 days. On average, UFC excretion decreased by 44.5% compared with baseline. Overall, UFC decreased in 22/29 patients and five patients (17%) reached normal UFC excretion after 15 days of treatment (Boscaro et al. 2009). The results of a large, multicenter phase III study, in which the long-term efficacy of pasireotide was examined, have recently been published (Colao et al. 2012). In this study, 162 patients were included and randomized to treatment with pasireotide s.c. in a dose of either 600 or 900 µg twice daily. After 3 months of treatment, these dosages were increased by 300 µg (to either 900 or 1200 µg twice daily) in patients in whom UFC excretion did not fall below two times the upper limit of normal (ULN) or, in case baseline UFC excretion did not exceed two times ULN, in whom UFC had increased after 3 months compared with baseline. On average, UFC excretion decreased by 48% after 6 months of treatment (Fig. 1; Colao et al. 2012). Without needing up-titration of the dose of pasireotide, 33 patients (20.4%; 14.6% in the 600 µg group and 26.3% in the 900 µg group) reached normal UFC excretion levels after 6 months (Colao et al. 2012). Parallel with the decrease in UFC, improvements were observed in blood pressure, weight, and quality of life (Webb et al. 2008, Colao et al. 2012). Hyperglycemia was the most important adverse event in this study, as glycated hemoglobin levels increased from 5.8 to 7.2% or 7.4%, depending on the dosage of pasireotide used. Other side effects included abdominal discomfort, headache, and cholelithiasis (Colao et al. 2012). Pasireotide was recently approved in the EU for treatment of CD after unsuccessful surgery.

Thus, monotherapy with either cabergoline or pasireotide induces complete biochemical remission in about 25% of patients. We performed a prospective open-label trial in which 17 patients with CD were treated in a stepwise manner with pasireotide mono or combination therapy with cabergoline and low-dose ketoconazole during 80 days (Feelders et al. 2010a,b).
The rationale of this approach was that the majority of corticotroph adenomas do co-express sst₅ and D₂R (de Bruin et al. 2009b) and that combined treatment with sst₅ and D₂R targeting compounds may have synergistic effects (Rocheville et al. 2000, Baragli et al. 2007). All patients started with pasireotide monotherapy in a dosage of 100 mg s.c. thrice daily. After 10 days, this dosage was increased to 250 mg s.c. thrice daily in case UFC excretion remained elevated. UFC excretion was measured again at day 28, after which, in case of persistent hypercortisolism, cabergoline (1.5 mg every other day) was added to pasireotide. If UFC remained elevated at day 56, ketoconazole (200 mg thrice daily) was added to pasireotide and cabergoline. Using this treatment regimen, 15/17 patients (88%) achieved biochemical remission after 80 days. As can be seen in Fig. 2, patients with more severe hypercortisolism at baseline needed more drugs to normalize UFC excretion (Feelders et al. 2010a,b). Apart from biochemical remission from CD, decreases in weight and blood pressure were observed (Feelders et al. 2010a,b). Again, hyperglycemia was the most important side effect; glycated hemoglobin levels increased from 5.8 to 6.7% after 80 days of treatment. Moreover, nine patients were insulin-like growth factor 1 (IGF1) deficient at the end of the study period (Feelders et al. 2010a,b). In ‘Pituitary-targeted drugs’ section, it was described that the expression level of the sst₂ is relatively low in corticotroph pituitary adenomas, probably due to downregulating effects of high concentrations of circulating glucocorticoids. After pasireotide mono or combination therapy, a subset of patients was operated and in vitro studies showed that sst₂ mRNA expression levels of adenomas from these patients, who were all in remission, were

**Figure 1** Urinary free cortisol excretion levels at baseline and after 6 months of treatment with pasireotide. Urinary free cortisol was available at baseline and at month 6 in a total of 103 patients; 61 patients had a reduction of at least 50% in urinary free cortisol levels at month 6. The black dashed line represents the upper limit of the normal range (ULN; 145 nmol/24 h (52.5 µg/24 h)). Reproduced with permission from Colao A, Petersenn S, Newell-Price J, Findling JW, Gu F, Maldonado M, Schoenherr U, Mills D, Salgado LR & Biller BM 2012 A 12-month phase 3 study of pasireotide in Cushing’s disease. *New England Journal of Medicine* 366 914–924.

**Figure 2** Mean levels of urinary free cortisol in five patients treated with pasireotide monotherapy, four patients treated with combination therapy with pasireotide plus cabergoline, and eight patients treated with pasireotide plus cabergoline and ketoconazole. Cabergoline was added to pasireotide if the level of urinary free cortisol had not normalized at day 28. Ketoconazole was added to pasireotide and cabergoline at day 60 if the patient had persistent hypercortisolism. The upper limit of the normal range is indicated by the dashed line. Bars indicate the S.E.M. Reproduced with permission from Feelders RA, de Bruin C, Pereira AM, Romijn JA, Netea-Maier RT, Hermus AR, Zelissen PM, van Heerebeek R, de Jong FH, van der Lely AJ et al. 2010b Pasireotide alone or with cabergoline and ketoconazole in Cushing’s disease. *New England Journal of Medicine* 362 1846–1848.
significantly higher than those of adenomas from patients with elevated preoperative UFC excretion (Feelders et al. 2010a). This suggests that glucocorticoid-induced sst2 downregulation is a dynamic process that might be reversed by cortisol-lowering therapy. One preliminary study describes a further decrease in UFC in four ketoconazole-treated patients after addition of octreotide (Vignati & Loli 1996). It might thus be an interesting concept to treat CD patients with cortisol-lowering therapy, which, in case of reappearing sst2 expression, is followed by treatment with a sst2 targeting somatostatin analog. Future studies should investigate the efficacy of such a treatment regimen.

With respect to adrenal blocking drugs, ketoconazole, metyrapone, and mitotane are most frequently used for CD. In a retrospective study, ketoconazole treatment, in a dose between 200 and 1000 mg/day, resulted in control of hypercortisolism in 17 out of 33 patients within 3 months with a concomitant clinical improvement. In five other included patients, ketoconazole was stopped within the first week of treatment because of intolerance (Castinetti et al. 2008). One older study with 28 patients showed that ketoconazole treatment was successful in 93% of patients, but this result was biased as patients had been treated before with radiotherapy (Sonino et al. 1991). Metyrapone, at dosages between 750 and 6000 mg/day, can effectively control cortisol overproduction in ~75% of patients during short-term treatment, i.e. up to 16 weeks, whereas long-term treatment resulted in biochemical remission in about 80% of patients, although these patients were also treated with radiotherapy (Verhelst et al. 1991). Mitotane, at lower dosages, can be useful in the treatment of CD (Luton et al. 1979, Schteingart et al. 1980, Kamenicky et al. 2011). Schteingart et al. (1980) reported clinical and biochemical remission of CD in 80% of patients treated with mitotane and pituitary irradiation. Another study showed control of hypercortisolism using mitotane monotherapy in 38/46 patients, whereas mitotane and pituitary irradiation combination therapy was successful in 100% of patients (Luton et al. 1979). Mitotane has, however, multiple side effects, which may limit long-term use.

Very recently, the efficacy of LCI699, a novel inhibitor of 11β-hydroxylase, was evaluated in 11 patients with CD at a dose of 2–50 mg twice daily. After 10 weeks of treatment, 8/9 patients that completed the study period had normalized UFC excretion (Bertagna et al. 2012). Like other adrenal-targeted drugs, this novel compound obviously does not target the cause of the disease in these patients. The clinical applicability and optimal dosage of LCI699 have to be further elucidated.

**Figure 3** Changes in glucose-related outcomes in patients with Cushing’s syndrome after treatment with mifepristone at dosages between 300 and 1200 mg daily. (A) HbA1c significantly decreased from baseline to week 24 or early termination (ET; \( P < 0.001 \)); (B and C) a significant reduction in area under the curve (AUC) for insulin (B) and significant improvements in homeostatic model assessment of insulin resistance (HOMA-IR; C) were also observed. Data are shown as mean ± s.d. To convert insulin values to picomoles per liter, multiply by 6.945. Reproduced with permission from Fleseriu M, Biller BM, Findling JW, Molitch ME, Schteingart DE & Gross C 2012 Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing’s syndrome. Journal of Clinical Endocrinology and Metabolism 97 2039–2049.
A recently published study by Fleseriu et al. showed beneficial effects of treatment with the GR antagonist mifepristone. In this study, 50 patients with CS (43 with CD) were treated for 24 weeks with mifepristone at dosages between 300 and 1200 mg daily (Fleseriu et al. 2012). Clear metabolic improvements were achieved with this treatment, as reflected by decreased glucose levels after oral glucose tolerance tests, decreased glycosylated hemoglobin levels, and increased insulin sensitivity (Fig. 3). Moreover, body weight significantly decreased and quality of life significantly improved after 24 weeks of treatment. As was expected, plasma concentrations of ACTH and cortisol increased at least twofold in 72% of the patients with CD. This illustrates the most important drawback of this treatment, as therapy with mifepristone does not target the pituitary adenoma. In this study, only one patient experienced an increase in adenoma size after 24 weeks of treatment, but as the authors emphasize in their paper, it is uncertain whether the risk of tumor growth increases with longer treatment duration. Frequently encountered adverse effects included fatigue, headache, abdominal discomfort, decreased serum potassium, and peripheral edema (Fleseriu et al. 2012). Mifepristone was recently approved in the U.S. for the treatment of hyperglycemia in patients with CS and type II diabetes if surgery is not an option or unsuccessful. Mifepristone might also be used to treat patients with CS that have an acute psychosis, in order to rapidly counteract the GR-mediated effects (van der Lely et al. 1991).

The optimal order and combination of drugs to treat CD is not known yet. Pasireotide and cabergoline have the advantage that they both target the underlying pituitary adenoma. However, the hyperglycemic effects of pasireotide are a point of concern for long-term treatment in a condition that is already accompanied by glucose intolerance. Further study on the mechanism and management of pasireotide-induced hyperglycemia is clearly needed. The adverse event profiles of adrenal blocking drugs and mifepristone can limit their long-term use. It should be emphasized that patients with CD and moderate-to-severe hypercortisolism need combination therapy to control cortisol excess. In this respect, combination of pasireotide and cabergoline may have synergizing effects. Another rationale for combination therapy may be to use lower drug dosages in order to reduce side effects of either agent like in the study of Vilar et al. (2010) in which cabergoline was combined with low-dose ketoconazole. Finally, combination therapy is indicated when symptomatology requires rapid reversal of cortisol excess, e.g. in case of psychosis. Thus, a tailor-made approach should be aimed in each patient according to individual characteristics. For instance, a patient with poorly regulated diabetes mellitus should not be treated with pasireotide, whereas in a patient with severe hypertension and hypokalemia, metyrapone would not be the first choice.

**Ectopic ACTH syndrome**

As outlined in the ‘ACTH-dependent CS–Ectopic ACTH syndrome’ section above, EAS is frequently accompanied by severe hypercortisolism, which can lead to hypertension, hypokalemia, acute psychosis, and thromboembolic complications. In addition, due to immunosuppressive effects, these patients are at risk for (opportunistic) infections and can rapidly deteriorate because of overwhelming sepsis. Apart from maximal supportive therapy (i.e. treatment with an aldosterone receptor antagonist, thromboprophylaxis, and antibiotic prophylaxis), cortisol production or its tissue effects should aggressively be decreased.

Kamenicky et al. (2011) recently performed a study in which patients with severe CS were treated with medical combination therapy. In their series, 11 patients were included, four of which had CD and seven had EAS. Patients had severe (e.g. pulmonary, cardiovascular, or infectious) complications that needed immediate intervention. Treatment was initiated with mitotane (3 g/24 h) and, as mitotane...
has a slow onset of action, ketoconazole (800 mg/24 h) and metyrapone (2.25 g/24 h). These dosages were adjusted based on the clinical signs. Patients were reported to experience clear improvement of their Cushingoid features. Interestingly, UFC (near-) normalized in all patients within the first 3 days (Fig. 4; Kamenicky et al. 2011). This treatment regimen was generally well tolerated, but main side effects were gastrointestinal complaints, hypokalemia, and increases in cholesterol and liver enzyme values. Considering its efficacy, this approach might be an alternative to emergency bilateral adrenalectomy, in particular for critically ill patients in whom surgery (bilateral adrenalectomy) is contraindicated. Recently, Sharma and Nieman reported four patients with EAS in whom prolonged remission was achieved with ketoconazole mono- or combination therapy with mitotane and/or metyrapone. Interestingly, in two patients sustained remission was observed after cessation of ketoconazole and metyrapone, which may in part be explained by effects of these drugs on tumoral ACTH secretion (Sharma & Nieman 2012). Finally, in the intensive care setting, the anesthetic drug etomidate, at dosages between 0.1 and 0.3 mg/kg per h, can be used to rapidly suppress cortisol production in complicated EAS (Schulte et al. 1990).

Blockade of cortisol tissue effects with mifepristone administration can also be an efficacious treatment for EAS. A recently published retrospective study reported improvement of clinical signs in 15/20 patients with CS of different etiologies after treatment with mifepristone (Castinetti et al. 2009). Most of these patients could be controlled with daily mifepristone dosages between 400 and 800 mg. An advantage of mifepristone is its rapid onset of action. Indeed, in this retrospective cohort, psychiatric symptoms improved within a week in 4/5 patients (Castinetti et al. 2009). This paper also summarized earlier published case reports on mifepristone treatment showing clinical improvement in 9/9 patients with EAS. Dosages higher than 1000 mg/day seem to be associated with more side effects, in particular hypokalemia and clinical adrenal insufficiency (Castinetti et al. 2009). Glucocorticoid antagonizing therapy may also modulate sst2 expression of ACTH-producing neuroendocrine tumors. We recently described two patients with an occult bronchial neuroendocrine tumor in whom the initially negative somatostatin receptor scintigram became positive after

**Figure 5** [111In-DTPA0]octreotide and CT imaging results in a patient with ectopic ACTH production by a bronchial carcinoid before (A and B) and after 6 months of therapy with mifepristone (C, D and E). Before mifepristone therapy was started, CT scan (A) shows a small nodule in the right upper lung (white arrow), which was not visible at the [111In-DTPA0]octreotide scan (B). After 6 months of mifepristone therapy, the CT scan shows the same lesion (white arrow) in the right lung (C), which can now be visualized with a repeat [111In-DTPA0]octreotide scan that shows pathological uptake at the site of the lesion (D and E; black arrows). Reproduced with permission from de Bruin C, Hofland LJ, Nieman LK, van Koetsveld PM, Waaaijers AM, Sprij-Mooy DM, van Essen M, Lamberts SW, de Herder WW & Feelders RA 2012 Mifepristone effects on tumor somatostatin receptor expression in two patients with Cushing’s syndrome due to ectopic ACTH secretion. Journal of Clinical Endocrinology and Metabolism 97 455–462.
treatment with mifepristone during 6 and 12 months respectively (Fig. 5; de Bruin et al. 2012). These patients were subsequently operated and immunohistochemical studies showed strong sst₂ expression. This observation demonstrates that glucocorticoid-mediated suppression of sst₂ expression can be reversed by blockade of the GR. Further studies are needed to evaluate whether glucocorticoid-antagonizing or -lowering therapy can improve the diagnostic yield of somatostatin receptor scintigraphy and can increase therapeutic efficacy of sst₂-preferring compounds.

These somatostatin analogs can be of use in the treatment of EAS when sst₂ is sufficiently expressed, although treatment escapes have been described (Hofland & Lamberts 2003). Dopamine receptors can also be expressed by ACTH-producing neuroendocrine tumors, and in small case series, complete responses were observed after treatment with cabergoline, either as monotherapy (Pivonello et al. 2007) or in combination with the sst₂-preferring somatostatin analog lanreotide (Pivonello et al. 2005). Further studies should further explore the efficacy of combined targeting of sst₂ and D₃R in EAS.

In summary, EAS that is complicated by severe CS should be treated aggressively. If patients cannot undergo curative or palliative surgery, medical therapy should be applied with mifepristone or combination therapy with inhibitors of steroidogenesis according to individual patient characteristics (e.g. presence of psychosis and disturbed liver function). In selected cases, somatostatin analogs and dopamine agonists may be effective. Further studies are needed on the optimal combination and doses of available drugs in the treatment of EAS.

**ACTH-independent CS**

Medical treatment in ACTH-independent CS is predominantly used for cortisol-producing ACC to treat acute complications of CS and/or in patients with advanced disease. Mitotane is the first-choice treatment for ACC considering its antiproliferative and antisecretory effects (Veytsman et al. 2009, Fassnacht et al. 2011). When hypercortisolism cannot be controlled by mitotane monotherapy or when the late-onset effects of mitotane cannot be awaited for, other adrenal blocking drugs, e.g. ketoconazole or metyrapone, or the GR antagonist mifepristone can be added (Castinetti et al. 2009, Fassnacht et al. 2011). In case of progressive disease under mitotane treatment, chemotherapy with etoposide, doxorubicin, and cisplatin can be considered (Fassnacht et al. 2012), although there might be a high risk on infections in the neutropenic phase because of the hypercortisolemic state. Currently, tyrosine kinase inhibitors, IGF-1 receptor blockers, and interferon-β are evaluated in *in vitro* and/or *in vivo* models of ACC.

As outlined in ‘Adrenal adenoma and bilateral adrenal hyperplasia’ section, AIMAH is usually treated by bilateral adrenalectomy, whether or not preceded by medical therapy with steroidogenesis inhibitors. However, the identification of ectopic hormone receptors in AIMAH may provide perspectives for specific medical treatment by targeting the involved receptor or production of the endogenous ligand (Lacroix 2009). For instance, in AIMAH associated with catecholamine-responsive CS, treatment with β-adrenergic receptor antagonists can result in sustained control of cortisol overproduction (Lacroix et al. 1997). In AIMAH with ectopic LH receptor expression, inhibition of LH production with long-acting leuprolide acetate successfully reversed hypercortisolism (Lacroix et al. 1999), whereas in patients with food-dependent CS due to ectopic expression of the glucose-dependent insulino tropic peptide (GIP) receptor, treatment with octreotide led to biochemical improvement via inhibition of postprandial GIP release.

**Table 5** Medical treatment options for identified aberrant adrenal hormone receptors using an *in vivo* screening protocol in AIMAH

<table>
<thead>
<tr>
<th>Aberrant receptor</th>
<th><em>In vivo</em> screening protocol</th>
<th>Medical treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIP receptor</td>
<td>Mixed meal; oral glucose</td>
<td>Octreotide; GIPR antagonist</td>
</tr>
<tr>
<td>Vasopressin receptor</td>
<td>Upright posture</td>
<td>Vasopressin receptor antagonist</td>
</tr>
<tr>
<td>Administration of arginine vasopressin or desmopressin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Adrenergic receptor</td>
<td>Upright posture; isoproterenol infusion</td>
<td>β-Blockers</td>
</tr>
<tr>
<td>LH/hCG receptor</td>
<td>GNRH administration; hCG, recombinant LH</td>
<td>Long-acting GRNH agonist</td>
</tr>
<tr>
<td>5-HT4 receptor</td>
<td>Administration of 5-HT4 agonists</td>
<td>5-HT4 receptor antagonist</td>
</tr>
<tr>
<td>AT-1 receptor</td>
<td>Upright posture; angiotensin infusion</td>
<td>AT-1 receptor antagonist</td>
</tr>
</tbody>
</table>

GIP, glucose-dependent insulino tropic peptide; GIPR, GIP receptor; hCG, human chorionic gonadotropin; 5-HT4, serotonin; AT-1, angiotensin I. Reproduced with permission from Lacroix A 2009 ACTH-independent macronodular adrenal hyperplasia. 
*Best Practice & Research. Clinical Endocrinology & Metabolism* 23 245–259.
(Table 5; Reznik et al. 1992, de Herder et al. 1996). Thus, specific medical therapy for AIMAH can be considered after screening for aberrant receptors, although further study is needed on long-term efficacy of different treatment modalities. In this respect, a possible role for medical therapy in AIMAH associated with subclinical CS should also be examined.

Conclusions and future developments

Although surgery is still the primary treatment of most cases of CS, recent years have brought several developments in the medical treatment of different causes of CS. In CD, pituitary-targeted therapy with cabergoline and pasireotide has been shown to be efficacious in ~20–40% of patients with CD when used as monotherapy. Higher success rates have been obtained not only by combination therapy with pasireotide, cabergoline, and ketoconazole but also by combining only cabergoline and ketoconazole. GR antagonizing therapy with mifepristone can result in rapid clinical and metabolic improvement. Preclinical studies with retinoic acid and the EGFR-directed tyrosine kinase inhibitor gefitinib have shown promising results, but future studies should examine their clinical applicability.

With respect to ACTH-independent macronodular adrenal hyperplasia, an increasing amount of data has become available showing promising results of drugs targeting different aberrantly expressed receptors at the level of the adrenal cortex. Such receptor-directed therapy could be an alternative to bilateral adrenalectomy in these patients.

Medical therapy for CS should be given with a tailor-made approach, involving relevant patient characteristics, in which potential clinical efficacy of a drug should be carefully weighed against its potential side effects.

Declaration of interest

R A Feelders and W W de Herder have performed consultancy activities for Novartis.

References


de Bruin C, Feelders RA, Waaijers AM, van Koetsveld PM, Sprij-Mooij DM, Lamberts SW & Hofland LJ 2009a Differential regulation of human dopamine D2 and...


Feelders RA, De Bruin C, Pereira AM, Romijn JA, Netea-Maier RT, Hermus AR, Zeliss PM, Sprij-Mooij D, Van der Leij AJ, De Herder WW et al. 2010a Medical treatment of Cushing’s disease with pasireotide mono- or combination therapy with cabergoline and ketoconazole modulates somatostatin receptor subtype expression on corticotroph tumor cells. Endocrine Reviews 31 (Supplement 1) S845 abstract OR14-6.


R van der Pas et al.: Developments in the medical treatment of CS

www.endocrinology-journals.org

Downloaded from Bioscientifica.com at 04/20/2019 02:45:57PM via free access


Received in final form 18 August 2012
Accepted 30 August 2012
Made available online as an Accepted Preprint 30 August 2012