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Mini-Review

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Adrenally Directed Medical Therapies for Cushing Syndrome

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Abbreviations: ACTH, adrenocorticotropin; CD, Cushing disease; CS, Cushing syndrome; UFC, urinary free cortisol.

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Abstract

Context: Endogenous Cushing syndrome (CS) is characterized by excess cortisol secretion, which is driven by tumorous secretion of corticotropin in the majority of patients. Untreated, CS results in substantial morbidity and mortality. Tumor-directed surgery is generally the first-line therapy for CS. However, hypercortisolism may persist or recur postoperatively; in other cases, the underlying tumor may not be resectable or its location may not be known. Yet other patients may be acutely ill and require stabilization before definitive surgery. In all these cases, additional interventions are needed, including adrenally directed medical therapies.

Evidence Acquisition: Electronic literature searches were performed to identify studies pertaining to adrenally acting agents used for CS. Data were abstracted and used to compile this review article.

Evidence Synthesis: Adrenally directed medical therapies inhibit one or several enzymes involved in adrenal steroidogenesis. Several adrenally acting medical therapies for CS are currently available, including ketoconazole, metyrapone, osilodrostat, mitotane, and etomidate. Additional agents are under investigation. Drugs differ with regards to details of their mechanism of action, time course of pharmacologic effect, safety and tolerability, potential for drug-drug interactions, and route of administration. All agents require careful dose titration and patient monitoring to ensure safety and effectiveness, while avoiding hypoadrenalism.

Conclusions: These medications have an important role in the management of CS, particularly among patients with persistent or recurrent hypercortisolism postoperatively or those who cannot undergo tumor-directed surgery. Use of these drugs mandates adequate patient instruction and close monitoring to ensure treatment goals are being met while untoward adverse effects are minimized.

Freeform/Key Words: Cushing syndrome, etomidate, ketoconazole, metyrapone, mitotane, osilodrostat

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Endogenous Cushing syndrome (CS) is associated with substantial morbidity and mortality, which can be mitigated by abrogating cortisol excess (1-5). Definitive treatment of CS is directed at resecting the underlying lesion driving hypercortisolism, including a corticotropin-secreting pituitary adenoma in 70%, an ectopic tumor secreting corticotropin in 10%, or an adrenal lesion (adenoma, carcinoma, or hyperplasia) in 20% of patients (4).

Although tumor-directed surgery is the first-line treatment for CS, it is clear that medical therapy also has a significant, albeit adjunctive, role in the care of these patients. Among patients with corticotroph adenomas (Cushing disease; CD), pituitary surgery may not result in endocrine remission in 10% to 20% of cases, or recurrence may occur despite initial remission in 20% to 30% of patients on long-term follow-up (6-8). In other patients, the ectopic tumor location may be unknown despite extensive evaluation, whereas in others the primary tumor may not be fully resectable (eg, in some patients with metastatic neuroendocrine tumors).

Medical therapy is indicated for patients with CS who have persistent or recurrent hypercortisolism after surgery or those who are not surgical candidates (4). In some cases, medical therapy can be administered preoperatively to control hypercortisolism toward improving the clinical status of patients in anticipation of surgery. Acutely ill patients, including those with severe infections (sepsis and sinusitis, among others), recent cardiovascular events (myocardial infarction or pulmonary embolism), or acute psychosis, generally require stabilization with medical therapy directed at controlling hypercortisolism before they can safely undergo tumor-directed surgery for CS. Medical therapies for CS include adrenally directed therapies, medications directed at corticotropin-secreting tumors, and drugs that inhibit the glucocorticoid receptor (3, 4).

The aim of the present review article is to discuss adrenally directed therapies for CS. To identify pertinent articles, electronic literature searches were conducted using the keywords *Cushing syndrome*, *medical therapy*, *steroidogenesis inhibitor*, *ketoconazole*, *metyrapone*, *osilodrostat*, *mitotane*, etomidate, and *levoketoconazole*. Articles were cited at the discretion of the author.

Ketoconazole, metyrapone, osilodrostat, mitotane, and etomidate represent adrenally directed therapies presently in use for CS and inhibit one or several steps of adrenal steroidogenesis (Table 1 and Fig. 1). Among these agents, some have been used for decades based on observations from retrospective reports but have not been studied in

Table 1. Currently available adrenally directed medical therapies (steroidogenesis inhibitors) for Cushing syndrome

Agent	Mechanism of action	Dose range	Advantages	Limitations
Ketoconazole	Inhibits several adrenal steroidogenic enzymes	200–600 mg orally, 2×/d or 3×/d	Rapid onset of action[a]	Requires gastric acid for absorption; associated with hypogonadism in men; potential for rare but serious hepatotoxicity (regular monitoring advised); potential for drug-drug interactions
Metyrapone	Inhibits 11-β hydroxylase and aldosterone synthase	250-1000 mg orally 3×/d or 4×/d	Rapid onset of action[a]; has been used during pregnancy	Potential for mineralocorticoid and androgenic adverse effects
Osilodrostat	Inhibits 11-β hydroxylase and aldosterone synthase	1-30 mg orally 2×/d	Rapid onset of action[a]	Potential for mineralocorticoid and androgenic adverse effects; potential for drug-drug interactions
Mitotane	Inhibits several adrenal steroidogenic enzymes	0.5-3.0 g orally 3×/d	Cytolytic/cytotoxic[b]; useful activity in adrenocortical carcinoma	Slow onset of action (wks to mos); teratogenic and abortifacient; potential for drug-drug interactions
Etomidate	Inhibits 11-β hydroxylase and cholesterol side-chain cleavage enzyme	5 mg IV bolus, followed by infusion at 0.02-0.3 mg/kg/h	Only agent available for IV use; can control hypercortisolism within hours[c]	Requires careful monitoring for sedation

Several agents are used "off-label" for Cushing syndrome (see text for details).

Abbreviations: IV, intravenously; UFC, 24-hour urinary free cortisol.

[a]Monitor 24-hour UFC and serum cortisol every 3 to 7 days during the first month until stable, then every 2 to 3 months or after dose changes.

[b]Monitor UFC every 2 weeks during the first 3 months until stable, then every 2 to 3 months or after dose changes.

[c]Monitor serum cortisol every 6 hours until stable, then daily or after dose changes.

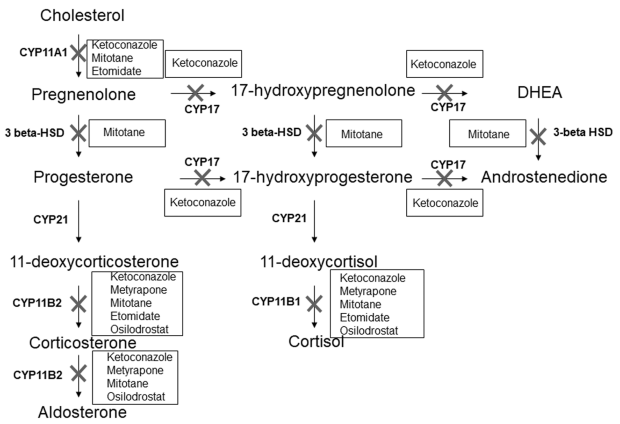

Figure 1. Site of action of adrenally directed medical therapies for Cushing syndrome. Both ketoconazole and levoketoconazole act on the same enzymes. 3 β-HSD; 3 β-hydroxysteroid dehydrogenase; CYP11A1, side-chain cleavage enzyme (desmolase); CYP11B1, 11 β-hydroxylase; CYP11B2, aldosterone synthase; CYP17, 17 α-hydroxylase/17, 20 lyase; CYP21A2, 21-hydroxylase; DHEA, dehydroepiandrosterone.

randomized clinical trials. However, there have been several recent developments in the field, leading to the regulatory approval of one agent for the treatment of subsets of patients with CS. Furthermore, a number of novel adrenally acting therapies are under investigation, as will be subsequently discussed.

Steroidogenesis inhibitors can control hypercortisolism regardless of the underlying cause of CS. These agents are generally titrated toward normalizing 24-hour urinary free cortisol (UFC) or serum cortisol (the latter is generally the case for patients being treated with etomidate) (9, 10). Limited data suggest that salivary cortisol may also be used to monitor therapy (11). Less frequently, steroidogenesis inhibitors are used at higher starting doses to block endogenous cortisol secretion completely while exogenous glucocorticoid replacement is administered. These so-called "block and replace" regimens can be particularly helpful in patients with cyclic hypercortisolism or those with very severe hypercortisolism. In addition, this approach is typically undertaken in patients on mitotane therapy. However, such a "block and replace" strategy requires careful monitoring to avoid cortisol excess occurring as a result of incomplete suppression of endogenous cortisol biosynthesis together with exogenous glucocorticoid administration. Frequent monitoring is recommended at the onset of therapy, particularly among hospitalized patients with severe hypercortisolism (see Table 1).

Escape from the salutary effects of some steroidogenesis inhibitors is possible in patients with CS, including some patients with CD, and occurs as a consequence of increased corticotropin secretion by the underlying pituitary tumor. Use of these agents requires careful patient monitoring to ensure clinical effectiveness and detect possible adverse events, including hypoadrenalism, which may occur as an extension of their pharmacologic action. Hypoadrenalism may be more common in patients with autonomous (corticotropin-independent) cortisol secretion from adrenal lesions who are treated with steroidogenesis inhibitors, since corticotropin is suppressed and is unlikely to override the steroidogenic blockade. Growth of a corticotroph adenoma may occur in patients with CD, necessitating periodic pituitary imaging in patients on long-term medical therapy with steroidogenesis inhibitors (12, 13).

Ketoconazole

Ketoconazole is an imidazole agent that possesses useful antifungal activity (14, 15). In addition, ketoconazole inhibits multiple steps involved in adrenal steroidogenesis (see Fig. 1) (16-20). It has been suggested that ketoconazole may also have direct inhibitory effects on corticotropin secretion but the clinical significance of this observation is uncertain (21). Ketoconazole is licensed as a treatment of CS in several European countries but is used "off label" in the management of patients with CS in the United States. The effectiveness of this agent in CS is supported by several retrospective studies (16, 17, 22-24). In one multicenter study, 200 patients with CD received ketoconazole monotherapy (median dose, 600 mg daily) in 14 centers in France over 17 years (22). Ketoconazole was reported to lead to UFC normalization in 49.3% of patients. An additional 25.6% of patients experienced a 50% or greater decline in UFC. Among 40 patients who were treated with ketoconazole preoperatively, 48.7% achieved UFC normalization. In addition, 40% to 50% of patients experienced improvements in glycemia, hypertension, and hypokalemia.

Ketoconazole requires the presence of gastric acid for absorption and may therefore be inadequately absorbed in patients with achlorhydria or those taking medications that decrease gastric acid secretion (25, 26). It is advisable for such patients to take the medication with an acidic beverage toward improving oral absorption. Ketoconazole has the potential to interact with medications metabolized through or modulating the activity of the CYP3A4 enzymatic pathway. Medications that inhibit CYP3A4 (including itraconazole, clarithromycin, ritonavir, and others) may increase the bioavailability of ketoconazole, whereas those that induce CYP3A4 (such as rifampin, carbamazepine, phenytoin, and others) may decrease ketoconazole concentrations. As a consequence, review of all other medications concurrently taken by patients on this therapy is recommended.

In addition to hypoadrenalism, adverse events associated with ketoconazole use include headache, nausea, dyspepsia, pruritus, and skin rash. Hypogonadism and

gynecomastia may occur in men as a consequence of decreased testosterone secretion by the testes (18, 27). Ketoconazole use is ideally avoided during pregnancy because it may potentially interfere with the masculinization of a male fetus. Transaminitis is common but is generally asymptomatic and reversible on drug discontinuation or dose reduction (28). Mild elevations in transaminases occur in about 13% of patients but more severe transaminitis (> 5 × upper limit of normal) may also occur, albeit less frequently (22). Idiosyncratic, life-threatening hepatitis leading to liver failure may occur and has been reported in 1:10 000 to 1:15 000 patients treated with ketoconazole (29, 30). Regulatory authorities have mandated the insertion of a "black box" warning on the drug label, informing prescribers and patients of the risk of severe hepatitis associated with ketoconazole use and advising regular monitoring of hepatic chemistries in patients on this medication. Because of these concerns, the availability of ketoconazole has been limited in some countries.

Metyrapone

Metyrapone inhibits 11-β hydroxylase, the terminal enzyme involved in cortisol biosynthesis, thereby blunting cortisol secretion (see Fig. 1) (31). The drug also inhibits aldosterone synthase. Metyrapone is licensed for use as a therapeutic agent for CS in several European countries but is used "off label" in the United States for this indication. Retrospective studies have provided evidence supporting the effectiveness of metyrapone in controlling hypercortisolism (24, 31-34). In one multicenter study, 195 patients with CS of diverse etiologies (115 of whom had CD) were treated with metyrapone at 13 centers in the United Kingdom over 16 years, including 164 patients who received monotherapy (35). Patients were treated at a median metyrapone dose of 750 mg to 1500 mg daily (depending on the underlying cause of CS). Disease control was achieved in 43% (based on UFC normalization) and 55% of patients (based on cortisol day curve). Metyrapone has been used successfully during pregnancy to control hypercortisolism without evident fetal harm (36-38). However, the medication is not specifically licensed for use during gestation.

Besides hypoadrenalism, dizziness, nausea, and dyspepsia may occur and are often reversible on dose reduction. Taking the medication with food may also be helpful in minimizing gastrointestinal distress. Accumulation of adrenal steroid precursors with mineralocorticoid activity may occur, leading to hypertension, edema, or hypokalemia. Accumulation of androgenic steroid intermediates may also occur, presenting with hirsutism or acne in women. As a corollary, monitoring blood pressure, serum potassium, and testosterone levels is advised. Of note, cortisol levels are overestimated on testing by many immunoassays among patients receiving metyrapone therapy (39, 40). This artifact is a consequence of cross-reactivity between cortisol and 11-deoxycortisol in immunoassays and can be avoided by using tandem mass spectrometry to measure cortisol levels in patients on metyrapone therapy (39, 40). In addition, newer immunoassays that employ highly specific monoclonal antibodies show very low cross-reactivity between cortisol and 11-deoxycortisol and may be used to monitor therapy in these patients.

Osilodrostat

Osilodrostat decreases cortisol biosynthesis by inhibiting 11-β hydroxylase; the drug also inhibits aldosterone synthase (see Fig. 1) (41-43). Osilodrostat has been approved in the United States as well as several European countries as therapy for patients with pathologic hypercortisolism who have active disease after surgery or are not surgical candidates. In a phase 3 study, 137 patients with CD who had persistent or recurrent disease postoperatively or were not surgical candidates received treatment with osilodrostat for 24 weeks (44). During the study, 72 of 137 (53%) patients achieved UFC normalization at week 24 without osilodrostat uptitration after week 12 and were eligible for random assignment to either drug withdrawal or continued therapy for 8 weeks. A significantly higher proportion of patients on osilodrostat (86%) compared to those on placebo (29%) maintained normal UFC levels without undergoing dose uptitration during the randomized withdrawal phase. Subsequently, all study participants were eligible for osilodrostat therapy through week 48 of the study. By then, salutary effects on body weight, quality of life, blood pressure, and glycemia were reported. Other, smaller studies have reported that osilodrostat can be efficacious in controlling hypercortisolism in the majority of patients with CS of diverse etiologies (besides CD) (45, 46). Of note, osilodrostat therapy has not been studied during pregnancy. Available data do not establish the superiority of osilodrostat over metyrapone with regards to efficacy or safety in the absence of head-to-head studies.

As is the case in metyrapone-treated patients, cortisol should be measured by tandem mass spectrometry in patients receiving osilodrostat therapy (in light of the known cross-reactivity between 11-deoxycortisol and cortisol in immunoassays). Osilodrostat may interact with drugs metabolized through the CYP3A4, CYP1A2, CYP2C19, and CYP2D6 enzymatic pathways (47). Careful review of all medications taken concurrently by patients is advised and possible adjustments in osilodrostat dose need to be considered in such cases.

In addition to hypoadrenalism, adverse events associated with osilodrostat administration include headache, nausea, arthralgias, and dizziness. It is possible that such symptoms may represent hypoadrenalism or withdrawal symptoms from cortisol excess. Androgenic symptoms (hirsutism, acne) or mineralocorticoid manifestations (edema, hypertension, hypokalemia) may occur as a consequence of accumulation of adrenal steroid precursors with androgenic or mineralocorticoid activity, respectively. An asymptomatic decrease in neutrophil (white cell) count has been noted in some patients. In addition, minor QT prolongation may occur but no serious arrhythmias have been reported. It is advisable to correct electrolyte abnormalities, monitor blood pressure, serum electrolytes and testosterone levels, and obtain periodic electrocardiograms before and during therapy with osilodrostat. Avoiding medications that are associated with QT prolongation is also advisable.

Mitotane

Mitotane (o,*p*´, DDD) is chemically related to an older insecticide (DDT) and inhibits several enzymes involved in adrenal steroidogenesis (see Fig. 1). In addition, mitotane is adrenolytic when administered in higher doses for a prolonged period. Mitotane is approved for the treatment of adrenocortical carcinoma, for which it has been used as an adjunct to surgery to prolong progression-free survival in patients undergoing tumor resection (48, 49). Monitoring serum levels (every 2 weeks over the first several months until stable) is advisable to ensure adequate therapy in patients with adrenocortical carcinoma (50, 51). Mitotane therapy may also offer palliation in patients with adrenocortical carcinoma who have locally unresectable or metastatic disease. Mitotane has also been used in some countries as an off-label treatment of CD. In a retrospective study of 76 patients with CD who had not received previous pituitary radiotherapy and were treated with mitotane, UFC normalization was reported in 72% (48 of 67) patients on long-term therapy (mean dose, 2.4 g/daily) (12). Improvements in glucose and blood pressure were also reported. However, recurrence of hypercortisolism was noted in 71% (17 of 24) patients several months after treatment discontinuation.

Mitotane has a slow onset of action over several weeks and cannot be used as monotherapy in patients requiring urgent control of hypercortisolism. Hypoadrenalism frequently develops in patients on long-term mitotane therapy. As a corollary, glucocorticoid replacement is generally advised in patients on mitotane treatment. Mitotane raises serum cortisol-binding globulin levels, which may mask the presence of hypoadrenalism, when (total) serum cortisol levels are measured. Measuring free cortisol levels may be helpful in the endocrine assessment of patients on mitotane therapy (52). In addition, mitotane accelerates hydrocortisone clearance (53). As a consequence, glucocorticoid replacement has to be administered in higher than usual doses (generally twice as high as typical replacement doses) in patients on mitotane therapy (54). Mitotane also has the potential to interact with medications metabolized through the CYP3A4 pathway, necessitating careful review of all concurrent medications (55).

Mitotane is very lipophilic and is extensively stored in adipose tissue, from which it is slowly cleared after discontinuation. Mitotane is teratogenic and abortifacient. As a corollary, it is advisable for women to defer pregnancy for 5 years after mitotane discontinuation.

Besides hypoadrenalism, patients on mitotane therapy may develop a number of adverse effects, including gastrointestinal, hepatic (transaminitis), neurologic (headache, gait instability, dizziness, tingling, dysarthria), hematologic (neutropenia), bladder, ophthalmic, metabolic (dyslipidemia), and dermatologic toxicities, which may often limit patient tolerance and have prevented its widespread use in patients with nonmalignant etiologies of CS (56).

Etomidate

Etomidate is an intravenous agent used to induce anesthesia, which additionally inhibits 11-β hydroxylase but also inhibits the cholesterol side-chain cleavage enzyme (see Fig. 1) (57, 58). Administered even in subhypnotic doses, etomidate has been used off label to control severe hypercortisolism in acutely ill patients with CS of various etiologies (57, 59-61). It is the only agent currently available for intravenous use in CS and can be life-saving as a bridge to another intervention (typically surgery) in patients with prodigious hypercortisolism. In one study of 7 patients with severe CS, rapid biochemical control was achieved within hours in all but one patient who entered hospice care (62).

Etomidate therapy requires close monitoring in intensive care unit settings to detect and mitigate excessive sedation. Other possible adverse effects include nausea, vomiting, dystonia, and myoclonus. Some etomidate formulations contain propylene glycol, which can cause thrombophlebitis as well as dose-dependent acute renal injury and anion gap metabolic acidosis (63, 64). Administration through a central line may limit the occurrence of thrombophlebitis. Hemodynamic instability (hypotension, hypertension, bradycardia, or tachycardia) have been rarely reported.

Combination Therapy

Some studies have suggested a role for combination therapy in CS. However, the merits and indications for such a strategy are not well established. In one study, concurrent initiation of ketoconazole, metyrapone, and mitotane therapy in 11 patients with severe adrenocorticotropin (ACTH)-dependent hypercortisolism led to marked clinical improvement and rapid decline in UFC within 48 hours after initiation of therapy (65). After several months of combination therapy, it was possible to withdraw 7 patients from ketoconazole and metyrapone, while maintaining normal UFC on mitotane therapy alone. Eventually, 5 patients underwent tumor-directed surgery and entered remission. In another study, ketoconazole plus metyrapone therapy was administered to patients with severe CS, including 14 with ectopic ACTH-secreting tumors and 8 with adrenocortical carcinoma, leading to UFC normalization in 73% and 86% of patients, respectively, within several weeks (66). Therefore, it appears that combination therapy may facilitate disease control in selected patients with severe hypercortisolism and avert the need for urgent bilateral adrenalectomy.

In 2 other small studies of patients with CD, combination therapy with a steroidogenesis inhibitor and 1 or 2 centrally acting agents was reported (either ketoconazole plus cabergoline, or ketoconazole plus cabergoline and pasireotide) (67, 68). In each of the 2 studies, combination therapy led to biochemical control of hypercortisolism in a higher proportion of patients than single-agent therapy. However, more data are needed to fully characterize the subsets of patients that are most likely to benefit from combination therapy and identify the most effective treatment strategies.

Agents in Development

Several adrenally directed medical therapies have been in clinical or preclinical development, including levoketoconazole, nevanimibe (ATR-101), and abiraterone acetate. The use of fluconazole has also been reported in some patients with CS. In addition, the effects of a variety of agents have been reported in small numbers of patients with ACTH-independent CS who demonstrate aberrant expression of illicit receptors in adrenal lesions (69).

Levoketoconazole is the 2S, 4R enantiomer of ketoconazole and is being developed as a possible therapy in CS (70, 71). Preclinical data have suggested that levoketoconazole is more potent than its 2R, 4S enantiomer in inhibiting several enzymes involved in adrenal steroidogenesis and might also be less likely to cause hepatotoxicity (see Fig. 1) (70, 71). Levoketoconazole was administered to 94 patients with CS (80 of whom had CD) in a multicenter, open-label, single-arm, phase 3 study that involved a 5-month titration period and a 6-month maintenance period (72). During the titration phase, 62 of 77 patients (81%) achieved normal UFC. By the end of the maintenance period, 29 of 94 participants (31%) had UFC normalization without a dose increase during the maintenance phase (72). Improvements in body weight, depression, quality of life, glycemia, and serum lipids were also noted. Adverse events that were reported in the study include headache, nausea, hypoadrenalism, and QT prolongation. Reversible transaminitis (exceeding 3 × upper limit of normal) occurred in 10 individuals (11%). Severe hepatotoxicity (hepatic failure) was not reported. Available data cannot establish the superiority of levoketoconazole over ketoconazole with regards to efficacy or safety in the absence of head-to-head studies.

Fluconazole, another imidazole antifungal agent, has been of benefit in controlling hypercortisolism in case reports (73, 74). Fluconazole appears to be safer than ketoconazole and does not require gastric acid for absorption. Further studies are needed to establish its efficacy and safety in CS.

Nevanimibe is a selective inhibitor of acyl coenzyme A: cholesterol acyltransferase 1 (ACAT1), which catalyzes the esterification of cholesterol in the adrenal glands, and has been found to decrease serum cortisol levels in preclinical models of CS (75, 76). This drug has been under study in patients with CS of diverse etiologies, including adrenocortical carcinoma, for which it may additionally possess antitumor activity (77, 78). The drug has been also under investigation in congenital adrenal hyperplasia (79). However, data from a study in congenital adrenal hyperplasia showed limited efficacy and frequent gastrointestinal adverse events. A trial of nevanimibe in CS was recently terminated because of slow enrollment. The results have not been presented or published.

Abiraterone acetate is an inhibitor of 17-α hydroxylase and is an approved therapy for patients with metastatic prostate carcinoma (80, 81). Abiraterone acetate inhibits the synthesis both of cortisol and androgens (82). It also has cytotoxic effects in preclinical models of adrenocortical carcinoma (82). Abiraterone acetate was of benefit in a case report of a patient with adrenocortical carcinoma and severe CS (83). Abiraterone acetate is also being studied in patients with congenital adrenal hyperplasia.

Salutary biochemical responses to a variety of agents have been reported in small numbers of patients with CS secondary to adrenal pathologies, most often macronodular adrenal hyperplasia, whose adrenal lesions express illicit (aberrant) receptors, including β-adrenergic receptors, luteinizing hormone receptors, or glucose-dependent

Table 2. Factors that may influence the choice between therapeutic agents for Cushing syndrome

Factor	Notes
Need for rapid control of hypercortisolism in outpatients	Consider ketoconazole, metyrapone, or osilodrostat; consider combination therapy in patients with severe disease
Need for control of severe hypercortisolism in the hospital	Consider etomidate (especially if oral agents are contraindicated, ineffective, or poorly tolerated); otherwise, ketoconazole, metyrapone, or osilodrostat may be considered
Pregnancy	Metyrapone therapy has been most often used during pregnancy (not specifically approved for this indication)
Sex	Ketoconazole may be preferable in women; metyrapone may be preferable in men
Patients' comorbidities	Caution with use of drugs that are associated with QT prolongation in patients at risk
Concurrent medications	Ketoconazole, osilodrostat, and mitotane have potential for drug-drug interactions
Patients' preference and previous experience with medical therapies	
Patients' ability to adhere to recommendations for therapy and monitoring	
Cost	Newer agents are likely to be more expensive than older drugs, which could influence third parties' decision to cover their cost

insulinotropic peptide receptors (69, 84-87). In such cases, administration of β-adrenergic receptor antagonists, leuprolide, or somatostatin receptor ligands, respectively, may lead to (at least) transient control of hypercortisolism (88-90).

Summary

Several steroidogenesis inhibitors are currently available and have an important, albeit adjunctive, role in the management of patients with CS. In the absence of head-to-head clinical studies, a selection between different medications can be made on the basis of several criteria (Table 2). A number of agents are in development and may offer additional therapeutic options in the future. Osilodrostat and levoketoconazole may have possible advantages in comparison with metyrapone and ketoconazole, respectively, including a lower frequency of administration. However, whether the newer agents are safer or more efficacious than the respective older compounds remains uncertain in the absence of head-to-head studies. Improving our understanding of the molecular underpinnings that drive the tumors that underlie CS may ultimately lead to even more novel, rationally designed therapies for this serious condition.

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