Medical Therapy for Cushing’s Disease – Past and Future Modes of Treatment

Cushing’s disease is the most frequent cause of endogenous hypercortisolaemia. As in other cases of Cushing’s syndrome, the goals of treatment are the normalisation of cortisol levels with a reversal of clinical symptoms in order to avoid the long-term consequences of hypercortisols. Surgical removal of the adenoma is the current first-line therapeutic approach, which may be followed by radiotherapy in cases of surgical failure. When these treatments have failed, drugs represent the next step in therapy, although they do not play a role in primary therapy as in other types of secretory pituitary tumours such as prolactinomas or acromegaly. However, their utility is reflected by the necessity to treat glucocorticoid excess in order to reverse the metabolic consequences and poor healing in severely affected patients, and this may be required before surgery. In cases where surgical treatment fails, drugs are an alternative as monotherapy or in addition to radiotherapy while awaiting its delayed effects. Finally, medical treatment may be considered in patients who cannot be submitted to surgical procedures because of co-morbidities, or who are unwilling to receive other types of treatment.

The ideal drug for Cushing’s disease that targets the pituitary has not been found. Variable compounds with neuromodulatory properties, including dopamine agonists and somatostatin analogues, gamma-aminobutyric acid (GABA) agonists, serotonin antagonists and different nuclear hormone receptor ligands involved in hypothalamo-pituitary regulation (thiazolidinediones and retinoic acid), have been tested. On the other hand, compounds that target glucocorticoid synthesis (adrenal secretion inhibitors or adrenolytic drugs, such as aminoglutethimide, metyrapone, ketoconazole, etonidazole, mitotane or trilostane) or function (glucocorticoid antagonists: mifepristone) have so far been broadly used to control the deleterious effects of the hypercortisolaemic state. Those pharmaceutical agents will be summarised in this article.

Neuromodulatory Compounds

Somatostatin Analogues

Somatostatin (SST) is a neuropeptide whose actions are mediated through five different membrane-bound receptors (SSTR1–5). SSTR2, 4 and 5 inhibit cell proliferation via a phosphotyrosine-phosphatase-dependent pathway and interact with the mitogen-activated protein kinase pathway, although recent data suggest an additional interaction with a serine–threonine phosphatase. SSTR3 is cytotoxic and causes cell death or apoptosis through a phosphotyrosine-phosphatase-dependent mechanism and activation of the p53 and Bax proteins. Although the heterogeneity of the studies performed and the differences in methodology have resulted in some contradictory findings, human corticotroph adenomas express multiple SSTR subtypes, with 1, 2 and 5 being the most frequently found; both SSTR2 and 5 seem to be implicated in the regulation of adrenocorticotropic hormone (ACTH) release, but SSTR5 is considered to be the predominant receptor. In vitro studies of animal-derived and human corticotroph adenoma cell lines, native SST and octreotide, a predominantly SSTR2-selective ligand having moderate affinity for SSTR5, inhibit basal and stimulated adrenocorticotropic hormone (ACTH) secretion. However, in vitro studies support the fact that this inhibition is present when the corticotroph cells have been cultured in corticosteroid-free medium. In patients with Cushing’s disease most experience has been gained with octreotide; however, this has been proved to be virtually ineffective.

Pasireotide or SOM-230 (Novartis, Basel, Switzerland) is a new multiligand SST analogue that has high binding affinity to SSTR5 and 1, 2 and 3 subtypes. It was found to inhibit basal and stimulated ACTH release from human ACTH-secreting pituitary adenomas and the murine corticotroph tumour cell line AT-20 in vitro, without inhibiting AT20 cell proliferation, nor inducing apoptosis or inhibiting pro-opiomelanocortin synthesis, implying an action through a possible blockade of ACTH release or an increased breakdown of ACTH. The functional activity of pasireotide compared with octreotide has been found to be 30-, 11- and 158-fold higher on SSTR1, 3 and 5, respectively, and approximately seven-fold lower on SSTR2, being more potent compared with octreotide in inhibiting basal ACTH release. In vitro studies in both human ACTH-secreting adenomas and the murine AT20 cell line, pasireotide suppressed ACTH secretion and corticotroph-releasing hormone (CRH)-induced ACTH release more than octreotide. Pre-incubation with dexamethasone did not affect the ability of pasireotide to inhibit CRH-induced ACTH release, while the suppressive action of octreotide was virtually lost. Furthermore,
SST2A and 2B (but not SST5) messenger RNA (mRNA) levels were significantly suppressed after 24 and 48 hours of dexamethasone treatment. These findings imply a differential impact of glucocorticoids on the expression of the different SSTs, with SST2 being downregulated and SST5 resistant to corticosteroid modulation. Sensitivity to SST inhibition of ACTH secretion is possibly observed only when the physiological feedback regulation of ACTH release by glucocorticoids has been lost; this hypothesis is supported by the absence of any effect on ACTH levels after experimental infusions of natural SST or octreotide in normal individuals, as well as by their suppression in patients with adrenal insufficiency or adrenoleucodystrophy. A direct effect of glucocorticoids at the transcriptional level or on mRNA stability has also been suggested. Recently, pasireotide was shown to significantly suppress cell proliferation as well as ACTH secretion in human corticotroph tumours, but possibly via independent mechanisms since no correlation was found between these effects. Another mechanism for its action might be an indirect influence of growth by decreasing secretion of pituitary hormones and/or growth factors. Recently, the use of pasireotide in the treatment of Cushing’s disease was investigated in a phase II, open-label, single-arm, multicentre pilot study. Twenty-nine patients self-administered subcutaneous pasireotide 600µg twice daily for 15 days. Remission of urinary cortisol to within the normal reference range was demonstrated in 17.2% of patients and a reduction in urinary free cortisol levels in 75.8%, along with a reduction in serum cortisol and plasma ACTH levels. These encouraging results suggest that pasireotide may be a promising novel therapy for Cushing’s disease with both antisecretory and potential antiproliferative properties; it may also be that inhibiting ACTH release and subsequent cortisol levels via SSTR5 will restore SSTR2 function, and hence further aid ACTH inhibition.

**Dopaminergic Neuromodulators**

Dopamine is the predominant catecholamine neurotransmitter in the human central nervous system, acting via its receptors (D1–5). The D2 receptor is expressed in the anterior and intermediate lobe of the pituitary gland, showing variable and heterogeneous expression in 89% of all types of pituitary tumours. It has also been detected in 69% of silent or functioning ACTH-secreting pituitary tumours in one study and in more than 75% of such tumours in another; its presence has been correlated with the inhibitory effect of dopamine agonists on ACTH secretion in vitro. However, no specific binding of a dopamine agonist was demonstrated in some corticotroph pituitary tumours, and the D2 receptor was not demonstrated by 123I-epidepride and single-photon emission computed tomography (CT) imaging in Cushing’s disease or Nelson’s syndrome.

Dopaminergic modulation of ACTH secretion has been suggested to occur via regulation of hypothalamic CRH release in addition to direct inhibition of ACTH secretion by the corticotrophs. The dopamine agonist bromocriptine suppressed ACTH secretion from cultured human pituitary tumour cells and induced apoptosis in AtT-20 cells. In Cushing’s disease, bromocriptine treatment has shown variable results and its therapeutic potential is considered very limited. In different studies the effectiveness of bromocriptine has varied between 0 and 50%, with remission of urinary and/or plasma cortisol in up to 40% of patients in various case reports and small series, but probably far fewer than 10% of unselected patients respond to this therapy. Bromocriptine has also been considered in cases of cyclical Cushing’s disease, and its beneficial effect has been suggested to be a diagnostic tool for this peculiar disorder. Cabergoline has also been investigated and reported to inhibit ACTH secretion in vitro in cases with D2-receptor-positive cells. After three months of therapy with cabergoline at doses of 2.5–3.5mg/week, a decrease of greater than 50% in daily urinary-free cortisol level and a normalisation of cortisol production were observed in 60 and 40% of patients, respectively. In addition, cabergoline has been successfully used in a case of pituitary macroadenoma-secreting aberrant ACTH and in small series showing tumour shrinkage and a decrease in cortisol levels. On the other hand, a direct effect on peripheral cortisol secretion has not been identified. In a more recent study, it was demonstrated that cabergoline treatment at doses of 1–7mg/week were effective in controlling cortisol secretion for at least one to two years in more than one-third of patients with CD after failure of surgical treatment. The expression of the D2 receptor in 80% of corticotroph pituitary tumours and the effectiveness of cabergoline treatment in the normalisation of cortisol secretion in patients with Cushing’s disease justifies consideration of the use of cabergoline for controlling this disorder. However, the long-term consequences of dopamine agonists specifically cabergoline and their value, as well as their combination with SST receptor ligands such as pasireotide, require further investigation.

**Pasireotide may be a promising novel therapy for Cushing’s disease with both antisecretory and potential antiproliferative properties.**

**Other Neuromodulatory Compounds and Ligands of Different Nuclear Hormone Receptors**

Cyproheptadine is a histamine and serotonin antagonist with poor selectivity for receptor subtypes that also possesses anticholinergic activity. It has been assumed that direct serotoninergic central nervous system control modulates hypothalamic factors that promote ACTH secretion or that it exerts a direct inhibitory effect on CRH and vasopressin secretion from the hypothalamus. In clinical studies, the response rate in patients treated with cyproheptadine or the similar metergoline has been poor, as has been the case with the more selective serotonin antagonists ritanserin and ketanserin, however, more positive results have been reported in cases with resistant microadenoma or in cases with no evidence of adenoma on imaging that have been suggested to represent “hypothalamic” Cushing’s disease. It was predicted that up to 70% of patients with Cushing’s disease would respond to cyproheptadine treatment, but its variability in clinical effects, its sedative side effects and the increase in the appetite of patients observed limited its use. Despite the fact that these compounds may have a direct effect on signalling pathways in the corticotroph cell independent of any effect on neurotransmitters, this form of therapy is limited by its adverse effects having no role in the modern management of Cushing’s disease.

Sodium valproate (valproic acid) inhibits β-aminobutyric acid aminotransferase. In patients with epilepsy it was shown that it decreases ACTH levels, possibly inhibiting CRH and hence ACTH release. Placebo-controlled studies of the agent did not support its use as monotherapy, although its combination with inhibitors of cortisol secretion appeared to be beneficial. It is possible that it may alter...
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cortisol metabolism, indirectly affecting ACTH release, but it does not seem to be of value in the therapy of corticotroph tumours.

Retinoic acid is an effective compound in reducing ACTH plasma levels and tumour size in animal models, but no human clinical trial has yet been performed. In rodent models it decreases corticotroph secretion and proliferation, as well as in a canine model of Cushing’s disease, producing a significant decrease in ACTH and cortisol levels, amelioration of clinical signs, prolongation of survival and pituitary tumour shrinkage without obvious side effects. Retinoic acid is a ligand for Nur77/Nurr1 and possibly of activator protein 1 (AP-1), which are positive transcriptional regulators of the ACTH gene in ACTH-secreting cells. Proopiomelanocortin (POMC) stimulation by CRH is mediated by Nur77 and may also involve AP-1, and is inhibited by retinoic acid; in addition, a reduction of the CRH-stimulated POMC transcription was produced by mutation of the NurRE or AP-1-binding sites. Endogenous production of ACTH was reduced by retinoic acid in AtT-20 tumour cells but not in normal pituitary cells, suggesting that retinoic acid is not part of the normal physiological feedback mechanism. Genes that have been found to be differentially expressed in pituitary tumours might also be involved in the differential action of retinoic acid. In addition, retinoic acid inhibits ACTH- and corticosterone-secreting cell proliferation, and it is possible that other in vivo pathways independent of AP-1 or Nur77/Nurr1 contribute to this effect. Additional beneficial effects include the reduction of adrenal hyperplasia by direct inhibition of adrenal cell proliferation, reversal of skin atrophy and immunostimulation.

Peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonists (rosiglitazone and pioglitazone) have been suggested to be promising new agents specifically targeting pituitary tumours, based on in vitro and rodent models. However, recent small-scale clinical trials with rosiglitazone and pioglitazone have not shown any clear therapeutic effect in Cushing’s disease. PPAR-γ belongs to the family of nuclear hormone receptors and ligands for the nuclear receptor and had been shown to induce cell-cycle arrest and apoptosis in corticotroph tumour cells and tumour growth arrest in vivo in a mouse model, and to inhibit ACTH and corticosterone secretion from tumour cells. PPAR-γ expression has been described in both normal and adenomatous pituitary tissue. A more recent study using more sensitive methodology revealed that PPAR-γ receptor is only poorly expressed in human pituitary tissue; the authors were unable to detect any specific abnormality of PPAR-γ expression in corticotroph tumours, describing poor immunocytochemical expression in both normal pituitary and pituitary adenomas with only weak cytoplasmic staining.

Futhermore, rosiglitazone showed antiproliferative effects only at very high doses, and these were not blocked by a specific PPAR-γ antagonist. Combining these results with the lack of a consistent effect on ACTH and cortisol levels in controls or patients with Cushing’s disease after short- or long-term administration, it seems that the treatment of pituitary tumours with PPAR-γ agonists is unlikely to be worth pursuing, and any effect of rosiglitazone or pioglitazone is also unlikely to involve the PPAR-γ receptor.

Inhibition of Cortisol Function

Glucocorticoid Antagonist

Mifepristone (RU 486) is a steroid that binds competitively to the glucocorticoid, androgen, and progesterin receptors and inhibits the action of the endogenous ligands. Its use in Cushing’s disease has been limited. Assessment of responsivity and dose monitoring is difficult, since the drug interferes with the glucocorticoid negative feedback at the hypothalamo–pituitary level and induces a rise in ACTH and cortisol secretion. This renders any assessment of response subject to clinical appraisal, while the blockade of cortisol receptors and loss of feedback necessitates frequent imaging, limiting its use as monotherapy in Cushing’s disease. Interestingly, it has been used in one patient with an ACTH-secreting pituitary macroadenoma after radiation therapy who responded extremely well to high doses (up to 25mg/kg daily) with remission of life-threatening clinical symptomatology. Potential adverse effects that have been reported in patients treated with high-dose mifepristone for long periods include adrenal insufficiency with difficulty in biochemical confirmation, as well as severe hypokalaemia attributed to excessive cortisol activation of the mineralocorticoid receptor that required treatment with spironolactone. Further evaluation of its safety and of follow-up methodology may render this agent a more attractive option, and clinical trials in the ectopic ACTH syndrome are currently under way.

Inhibition of Cortisol Secretion

These compounds decrease cortisol levels by direct inhibition of steroidogenesis at one or more enzymatic steps, being highly effective in treating hypercortisolism but not the underlying tumour, and they do not restore normal HPA secretory dynamics. Ketoconazole and metyrapone are the most frequently used drugs, and appear to be more effective and better tolerated than aminogluthethimide. All of these drugs require escalation after an initial low dose to minimise their side effects, and frequent monitoring is required to achieve an acceptable clinical and biochemical profile. The inhibition can be partial or complete, requiring a ‘block-and-replacement’ scheme. In either case, patients should be well instructed about adrenal insufficiency symptoms or the recurrence of hypercortisolism symptoms. In addition, there may be a requirement to increase the dose over time to maintain the desirable cortisol levels, since corticotroph tumours have a higher than normal set-point for cortisol negative feedback, and ACTH secretion may increase in parallel with the fall in cortisol. Occasional patients rarely remain in remission after their discontinuation when given as monotherapy.

Metyrapone blocks 11β-hydroxylase and has a rapid onset of action. It may be useful as monotherapy or in combination with other drugs, or following radiotherapy. Good control of cortisol levels is frequently obtained in both short- and long-term studies. In one case report a 13-year-old boy received a 2g regimen of metyrapone for four years with resolution of cushingoid features and a gain of 23cm in height, while a larger study of 53 patients reported effective short-term mean serum cortisol level control (1<400nmol/l) in 75% of patients with effective long-term control in 83% of the 24 patients (mean 2,250mg/day, median treatment duration 27 months) following pituitary irradiation. The rate of the positive results
from these studies is related to each study ‘cut-off’ values for ‘cortisol control’, however, it is generally accepted that metyrapone is a useful adjunctive treatment for Cushing’s disease.102 Interestingly, the block of adrenal steroidogenesis cannot be overcome even in cases with persistent increase of ACTH secretion along with the normalisation of cortisol levels.108–110 Metyrapone is given at an initial daily dose of 0.5–1g, in three to four divided doses, and may be increased every few days to a maximal daily dose of 6–8g.44,112,113 It has been used successfully pre-operatively, lowering mean cortisol levels to less than 400nmol/l with dose titration;111 the more recent target is a mean serum cortisol level below 300nmol/l.114 Since metyrapone results in increased ACTH secretion and thereby increased androgenic precursors with subsequent acne and hirsutism, this is a common cause of treatment discontinuation.103,108,111 The appearance of hypertension, hypokalaemia and oedema due to mineralocorticoid precursors are not serious side effects since cortisol levels are also reduced by the treatment.105,112,115 Other side effects include dizziness and gastrointestinal upset, although it is possible that some of these are in fact due to inadvertent induction of adrenocortical insufficiency.

Ketoconazole is an imidazole derivative that acts at a number of sites. It inhibits cytochrome P450 enzymes, with strongest effect on 17,20-lyase, and side-chain cleavage, 11β-hydroxylase and 17β-hydroxylase, but there is disagreement for the latter role.96,116,117 Interestingly, extra-adrenal actions have been reported. Ketoconazole caused an acute in vitro decrease in basal and CRH-stimulated ACTH secretion by corticotroph tumour cells obtained from two patients with Nelson’s syndrome,118 showing similar effects on rat anterior pituitary cells in vitro in one study119 but not in another.93 The fact that ACTH concentrations increase during long-term treatment with ketoconazole suggests that its major effect is on the adrenal cortex rather than the corticotroph cells. In addition, at high concentrations it has been shown to be an antagonist of the glucocorticoid receptor in cultured hepatoma cells120 and to bind to glucocorticoid receptors in cytosolic preparations of human mononuclear cells.121

A meta-analysis of 82 patients with presumed Cushing’s disease showed that monotherapy with ketoconazole at daily doses of 400–1,600mg effectively reduced serum cortisol levels by 70% (range 25–93%).122 It has also been administered as adjuvant treatment in conjunction with radiation therapy46 or in combination with other drugs such as octreotide, with equally satisfactory results.123 However, these trials are based on few patients or are biased by the co-administration of other treatments. Interestingly, when given to five women with presumed Cushing’s disease for three months, urinary cortisol excretion fell and plasma ACTH levels decreased by 30–75%.124 In another study, basal ACTH concentrations were increased compared with the pre-treatment values of four to six patients with presumed Cushing’s disease, and CRH-stimulated ACTH concentrations were increased in all, suggesting that ketoconazole may not suppress corticotroph tumors in vivo46 or that the elevation is due to a change in feedback.93 In the previous meta-analysis ACTH concentrations were increased by an average of 35% in patients in remission and 80% in patients with persistent disease. This limitation can be reversed by using additional adrenal enzyme inhibitors.55 Treatment with ketoconazole is usually started at a daily dose of 400mg (divided into two doses) and increased every three or more days to a maximum of 1.2–1.6g daily in three or four divided doses.44,117 As gastric acidity is necessary to metabolise it into the active compound, ketoconazole is not an option in achlorhydric patients or those treated with proton pump antagonists unless it is formulated locally in an acidic vehicle.44 An idiosyncratic hepatic dyscrasia occurs in about one in 15,000 cases, which has limited its use in occasional patients, and this may occasionally be fatal.125-129 Otherwise, it has a relatively benign spectrum of side effects such as gastrointestinal symptoms, gynaecomastia, irregular menses and reversible hepatic dysfunction, which do not necessarily require its discontinuation.44 Other noted side effects include decreased libido and impotence, probably owing to its inhibitory effects on 17β-hydroxylase and 17,20-lyase, which are the main cause of treatment discontinuation in men,112 the teratogenicity that contraindicates its use in pregnancy and its interactions with other medications because of the potent inhibitory effects on cytochrome P450 enzymes (particularly CYP3A4, CYP2C9 and CYP1A2). However, a recent clinical study in 38 patients supported the clinical value of ketoconazole as safe and efficacious treatment in CD, particularly in patients for whom surgery is contraindicated or delayed because of the absence of image of an adenoma on magnetic resonance imaging.130

Aminoglutethimide acts at a number of sites.131 It inhibits side-chain cleavage of cholesterol to pregnenolone and cortisol, oestrogen and aldosterone production,132,133 In addition, it inhibits 11β-hydroxylase, 18-hydroxylase and aromatase.134 It is not considered efficacious as monotherapy102,135 compared with its action as combination therapy,103,111 partly due to the feedback in ACTH, which negates its effect.135 It is given at a dose of 500mg daily in divided doses and can be increased by 250–500mg every three to four days to a total daily dose of 2g. In combination with metyrapone, it has been observed to be effective at up to one year at daily doses of 500–750mg together with 2g of metyrapone.111 In an original study of 33 patients with Cushing’s disease receiving a 250mg dosage three times daily, a clinical and biochemical remission rate of 42% were reported,102 but the authors concluded that bilateral adrenalectomy was preferable for continued biochemical remission. Neurological and gastrointestinal side effects and tolerance with continued treatment limit its use, although it has been stated that the presence of a transient morbilliform rash, fever and mild impairment of thyroid function are not reasons to discontinue therapy.123,111,137 Other side effects include dizziness, blurred vision, chorea and bone marrow suppression.44,138 In addition, aminoglutethimide is a strong inducer of several cytochrome P450 enzymes (including CYP1A2 and CYP3A4) with several drug interactions, including a fall in concomitant ketoconazole levels.99 Finally, the fact that it increases the metabolism of dexamethasone suggests that hydrocortisone is preferable if steroid replacement is needed.131,138 However, we believe that there is little place for this drug in the modern therapy of Cushing’s disease.

**Endogenous production of ACTH was reduced by retinoic acid in AtT-20 tumour cells but not in normal pituitary cells, suggesting that retinoic acid is not part of the normal physiological feedback mechanism.**

Etomidate is an imidazole derivative and, compared with ketoconazole, inhibits 11β-hydroxylase more potently, showing a similar inhibition of 17β-hydroxylase but a lesser effect on 17,20 lyase;137 in higher concentrations it has an effect on cholesterol side-chain cleavage.134,135 Blunting of the cortisol response to ACTH has been reported in vivo142,143 and inhibition of ACTH-stimulated cortisol secretion from dispersed adrenal
Trilostane blocks 3β-hydroxysteroid dehydrogenase and is a relatively weak inhibitor of steroidogenesis.\(^\text{143}\) Although it has been demonstrated to show beneficial effects in animal models,\(^\text{139}\) disappointing results have been reported in human trials and its use is not recommended.\(^\text{151}\)

Mitotane (O,P′DDD) inhibits steroidogenesis at the steps of side-chain cleavage, 11- and 18-hydroxylation and 3β-hydroxysteroid dehydrogenase.\(^\text{152–154}\) It has been considered to be highly effective in the long-term suppression of hypercortisolism in patients with Cushing’s disease because of its specific adrenolytic action. If used at high doses (greater than 4g per day) its metabolite binds macromolecules in adrenocortical cell mitochondria, leading to their destruction and cellular necrosis, resulting over time in permanent glucocorticoid and mineralocorticoid replacement therapy.\(^\text{44}\) Consequently, when 12g/day is used as monotherapy, remission has been observed in up to 83% of patients with Cushing’s disease, and was sustained after discontinuation in about one-third of them.\(^\text{155}\) It has been used moderately effectively as an adjunct to radiation therapy.\(^\text{9,156}\) with clinical and biological remission observed in 81% of 36 patients, with 47% ceasing long-term mitotane therapy.\(^\text{208}\) Four patients had no response, two had a partial response and the other patient died of an invasive pituitary malignancy. Mitotane is often started at 250–500mg nightly with slow escalation of the dose to 4–12g/day,\(^\text{89}\) and it is important to regularly monitor drug levels.\(^\text{171}\) The disadvantages of its use include a slow onset of action (weeks or months), a long half-life,\(^\text{156}\) significant gastrointestinal and neurological adverse effects, hypercholesterolaemia\(^\text{159}\) and less common problems such as gynaecomastia.\(^\text{44,150,113}\) When glucocorticoid and mineralocorticoid replacement therapy begins dexamethasone is an option because of its longer half-life, but its metabolism is induced by mitotane, requiring dose adjustments, whereas the metabolism of cortisol or prednisone is not.\(^\text{160}\)

However, mitotane induces a large rise in cortisol-binding globulin such that measurement of total cortisol is unreliable, and it is necessary to rely on plasma ACTH measurement or urinary free cortisol to avoid an adrenocortical crisis. Of note, patients under medical mitotane therapy are at risk of developing Nelson’s syndrome and pituitary radiotherapy is an option.\(^\text{209}\) In general, the problems associated with the use of mitotane determine that its use be confined to the minority of patients who are intolerant or not responsive to ketoconazole and/or metyrapone, and who are unsuitable for adrenalectomy.

Conclusions

An effective medical therapy that targets the pituitary adenoma would be a valuable therapeutic option for the management of Cushing’s disease; however, currently there is no effective medical therapy that directly and reliably targets the ACTH-secreting pituitary adenoma and thus the underlying cause of the disease. There are encouraging developments such as the somatostatin analogue pasireotide, from a phase II trial, and dopamine agonist cabergoline, from a long-term clinical study. The chimeric somatostatin-dopamine ligand dopastatin (developed to treat other types of pituitary tumour) may also show therapeutic promise in Cushing’s disease. It will also be of considerable clinical interest to design therapeutic trials with retinoic acid analogues. Consequently, since few currently available drugs are able to directly inhibit ACTH release and the fact that Cushing’s disease is the most frequent cause of endogenous hypercortisolism, therapy targeting the adrenal remains the mainstay of therapy. Worldwide experience with both ketoconazole and metyrapone (either alone or in combination) suggests that these agents are the most effective primary treatment for Cushing’s disease. However, the presence of hirsutism frequently precludes metyrapone therapy in women, while gynaecomastia or hypogonadism requires caution with the use of ketoconazole therapy in men, and the drug may be hepatotoxic; gastrointestinal symptoms may occur due to both compounds in both sexes. The difficulty in monitoring and the adverse effects of mitotane determine that its use be confined to the minority of patients not responsive or intolerant to ketoconazole and/or metyrapone. The other adrenal inhibitors are now rarely needed; however, etomidate remains an important option when intravenous administration is the only way of treating severely ill patients. Finally, mifepristone has been used in limited cases, but further evaluation of its safety and follow-up methodologies may render this agent a more attractive option. Nonetheless, if patients remain intolerant or incompletely responsive to medical therapy, it is extremely important to remember that bilateral laparoscopic adrenalectomy will cause immediate remission of hypercortisolism when all else fails.

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