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Advances in the medical management of Cushing's syndrome

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Background: Management of Cushing's syndrome, that is, excess cortisol secretion, has undergone considerable advances since the pioneering studies by Harvey Cushing. Surgery is clearly first choice for all etiologies of Cushing's syndrome, and medical therapy is largely administered in the interim between other therapeutic options. The limited use of medical therapy is a consequence of the lack of a truly efficacious compound to restrain adrenocorticotrophic hormone or cortisol secretion, but this will hopefully change in the near future as molecules developed over the past few years are tested. *Conclusion*: This paper illustrates present and perspective medical treatments for Cushing's syndrome.

Keywords: ACTH, bromocriptine, cabergoline, cortisol, Cushing's syndrome, ketoconazole, metyrapone, mitotane, pasireotide, retinoic acid, somatostatin, somatostatin analogues, steroidogenesis inhibitors, thiazolidinediones

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1. Introduction

Cushing's syndrome is a disease caused by different etiologies, has a fraught diagnostic work-up and one main treatment option, that is, surgery, with variable outcome. Etiology of endogenous hypercortisolism comprises adrenocorticotrophic hormone (ACTH)-dependent forms, represented by ACTH-secreting pituitary adenomas, also known as 'Cushing's disease' (85%), and ectopic ACTH-secreting neuroendocrine tumors (15%), and ACTH-independent forms, that is, cortisol-secreting adrenal adenomas, carcinomas or bilateral nodular hyperplasia, both congenital and acquired (**Table 1**). Clinical features of these distinct etiologies overlap and the differential diagnosis, as well as the diagnosis of Cushing's syndrome *per se*, require a battery of hormonal measurements supported by imaging procedures [1]. This review illustrates the advances in medical management of Cushing's syndrome and perspectives offered by recent research.

2. Therapeutic strategy in Cushing's syndrome

Once the etiological diagnosis has been established, any given patient with Cushing's syndrome is sent to the surgeon for removal of the causative lesion (**Figure 1**) [2,3]. Surgery is usually straightforward for benign adrenal lesions, whereas adrenal carcinomas, pituitary and extrapituitary ACTH-secreting lesions represent more complex issues. Adrenal carcinomas are highly malignant lesions with low survival rates, ameliorated by adjuvant therapy with mitotane and chemotherapy but still carrying an unfavorable prognosis. Pituitary surgery, aimed at removal of the ACTH-secreting adenoma, is the first-line therapy in Cushing's disease and, because pituitary adenomas are visible at imaging in only in 60% of patients, often requires a thorough pituitary exploration. However, even at the hands of the most experienced neurosurgeon, remission barely reaches 80% [4],

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Table 1. Etiology of Cushing's syndrome.

ACTH-dependent causes
Pituitary ACTH-secreting adenoma
Ectopic ACTH-secreting neuroendocrine tumors
ACTH-independent causes
Adrenal adenoma
Adrenal carcinoma
Bilateral adrenal hyperplasia:
Acquired with possible involvement of illicit receptors
Congenital: McCune-Albright syndrome, Carney's complex

thus one out of five patients will require further therapeutic maneuvers. In addition, some 20% of cured patients relapse, and they too will require further treatments. Options available to these patients include repeat pituitary surgery and radiation therapy (either radiosurgery or conventional pituitary irradiation) [5], but neither assures success in > 60% of patients, and, lastly, bilateral adrenalectomy. This latter approach has gained increasing acceptance since the advent of laparoscopic surgery, but leaves the patient dependent on lifelong steroid replacement therapy [6]. During this often tortuous therapeutic itinerary, drugs can be administered to contain cortisol hypersecretion and the attendant clinical manifestations. Lastly, patients with ectopic ACTH secretion may present two orders of problems: the tumor might not be completely resectable or, a not so rare occurrence, be 'occult', that is, not identifiable [7]. If surgery is not feasible or has failed, patients require adrenalectomy or medical therapy (**Figure 1**).

3. Medical treatment

Medical therapy, aimed at containment of excess cortisol secretion [8], is indicated in patients with Cushing's syndrome of any etiology in whom surgery has failed or is not a viable treatment option (**Figure 1** ; **Table 2**). The current treatment modality is inhibition of adrenal steroid synthesis with ketoconazole, an imidazole derivate, as the most widely used compound. Symptoms of cortisol excess can also be attenuated by interference with the tissue glucocorticoid receptor and, indeed, the antiprogestin RU486 has been used successfully in some cases. Although efficacious in all etiologies of Cushing's syndrome, ketoconazole and RU486 are targeted to downstream events and thus do not represent a causative approach to ACTH-dependent Cushing's syndrome. The use of drugs aimed at blocking adrenal stimulation by illicit receptors is limited to isolated case reports [9]. On the other hand, drugs aimed at controlling ACTH secretion by the pituitary or extrapituitary tumor, although theoretically preferable, have not proved fully satisfactory. All these compounds have been available for at least 10 years and developments mostly concern the use of sister molecules, for example cabergoline in place of bromocriptine, or of analogues with different specificities, such as the case for somatostatin, which are providing promising results. In addition, experimental studies are paving the way to future medical therapies with compounds such as thiazolidinediones and retinoic acid. This treatise will begin with drugs useful for all etiologies of Cushing's syndrome, then proceed to compounds specific to ACTH-dependent Cushing's syndrome.

Among these pharmacological options, patients are usually started on one compound, for example, ketoconazole, metyrapone or mitotane according to each center's preference and expertise, and, last but not least, drug availability. Etomidate is used only in severely ill patients who require immediate relief of symptoms. If single drug regimes prove unsatisfactory and other therapeutic options (i.e., surgery, radiation therapy) are still unavailable, then the addition of another drug may prove beneficial. Combination therapy with multiple adrenal steroid synthesis inhibitors offers the advantage of administering individual agents at lower doses, thereby reducing the risk of side effects. In the future, combined pituitary–adrenal blocking agents may become feasible as studies with cabergoline, somatostatin receptor agonists and other compounds yield convincing results.

3.1 Adrenal steroid synthesis inhibitors

These compounds are used primarily as antimycotics but share a common inhibitory activity on adrenal cytochrome P450 enzymes [10]. Steroidogenesis, in fact, requires the sequential action of three P450 enzymes and a dehydrogenase (**Figure 2**) and the blockade of one or more is sufficient to impair cortisol secretion. Partial or total inhibition of cortisol ensues according to the strength of the blockade and, indeed, adrenal insufficiency often occurs with potent steroid synthesis inhibitors, for example, metyrapone, etomidate and mitotane. Rebound ACTH increase may attempt to overcome the blockade and the use of progressively increasing doses is a common occurrence. Alternatively, multiple drugs may be administered at lower doses in order to avoid side effects related to high doses of a single compound. Medical therapy is also used as an extra measure in patients with Cushing's disease treated by radiation therapy and tapered over time as the full efficacy of radiation takes place. As mentioned above, few developments have occurred in the past few years with these drugs, with the exception of mitotane and etomidate.

3.1.1 Ketoconazole

Ever since the report by Sonino [11], the antimycotic ketoconazole has been used for containment of cortisol excess, and remains the most satisfactory drug for Cushing's syndrome. Ketoconazole blocks the first and last steps of cortisol synthesis (**Figure 2**), with an extra effect on 17 α-hydroxylase. No overwhelming ACTH rebound occurs on ketoconazole, and this has been explained by an additional

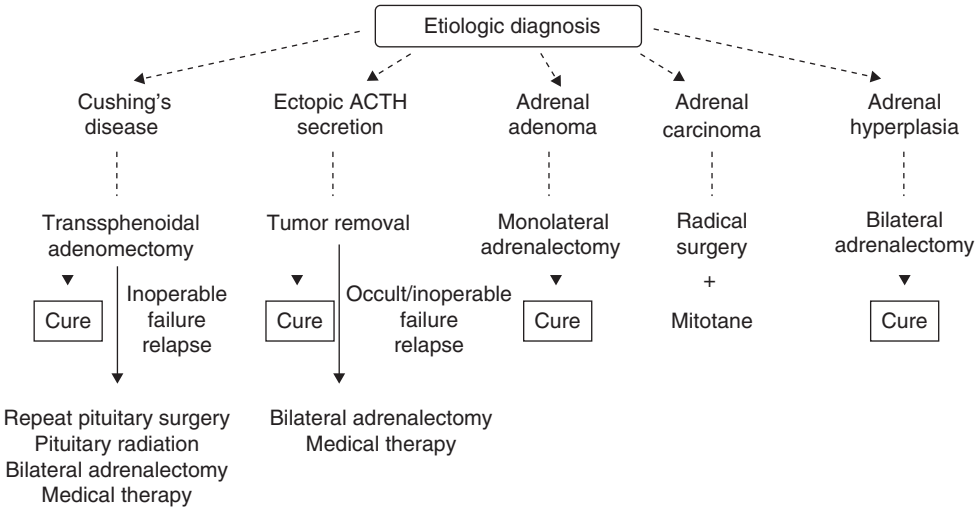

Figure 1. Therapeutic strategies for Cushing's syndrome. Treatment choices for each etiology of Cushing's syndrome are shown.

Table 2. Doses of drugs used for treatment of Cushing's syndrome.

Steroid synthesis blocking agents	
Ketoconazole	200 – 1000 mg/day
Fluconazole	200 – 400 mg/day
Metyrapone	500 – 6000 mg/day
Etomidate	0.03 – 0.3 mg/kg/h
Trilostane	240 – 1400 mg/day
Aminoglutethimide	1 – 2 g/day
Mitotane	0.5 – 5 g/day
Glucocorticoid receptor antagonist	
Mifepristone (RU486)	5 – 30 mg/kg/day (400 – 800 mg/day)
Serotonin receptor antagonists	
Ketanserin	40 – 80 mg/day
Ritanserin	10 – 15 mg/day
Cyproheptadine	12 – 24 mg/day
GABAergic agonists	
Sodium valproate	600 – 1000 mg/day
Dopamine receptor agonists	
Bromocriptine	2.5 – 40 mg/day
Cabergoline	0.5 – 7 mg/week
Somatostatin analogues	
Octreotide	100 – 200 µg/day
Octreotide LAR	30 mg/month
SOM230 (pasireotide)	1200 – 1800 µg/day
PPAR-γ agonists	
Rosiglitazone	8 – 16 mg/day
Pioglitazone	15 – 45 mg/day

inhibitory effect of ketoconazole on pituitary ACTH secretion [12]. Indeed, in the authors' experience, the effective dosage of ketoconazole is established after 2 – 3 weeks of treatment and maintained over time. A recent French retrospective study demonstrated normalization of urinary free cortisol (UFC) in 50% of patients treated with ketoconazole, accompanied by regression of some signs of hypercortisolism, such as hypertension, overweight and diabetes [13]. Another nitromidazole derivate, fluconazole, has recently been used in an elderly patient with cortisol-secreting adrenal carcinoma and achieved normalization of cortisol excretion for > 18 months [14], pointing to the possible efficacy of other, similar compounds.

3.1.2 *Metyrapone*

Metyrapone represents an alternative first choice medical therapy for Cushing's syndrome in some centers, but is not available worldwide. Both short-term and long-term treatments are efficacious, although most long-term reports in patients with Cushing's disease are in association with pituitary irradiation [15]. This drug has recently been used for control of hypercortisolism in pregnancy [16], McCune-Albright syndrome [17] and severe ectopic ACTH syndrome [18].

3.1.3 *Etomidate*

Etomidate, an anesthetic, belongs to the older generation of steroid synthesis inhibitors but has experienced a renewed interest over the past few years. Indeed, an increasing number of papers have been published on the use of intravenous etomidate to correct severe symptoms of hypercortisolism, both as an emergency drug and for long-term treatment. Etomidate inhibits both 11α-hydroxylase and 17α-hydroxylase (**Figure 2**) and can normalize serum cortisol within 12 h [19]. The advantages of etomidate are rapid reversal of hypercortisolism, intravenous administration – necessary for

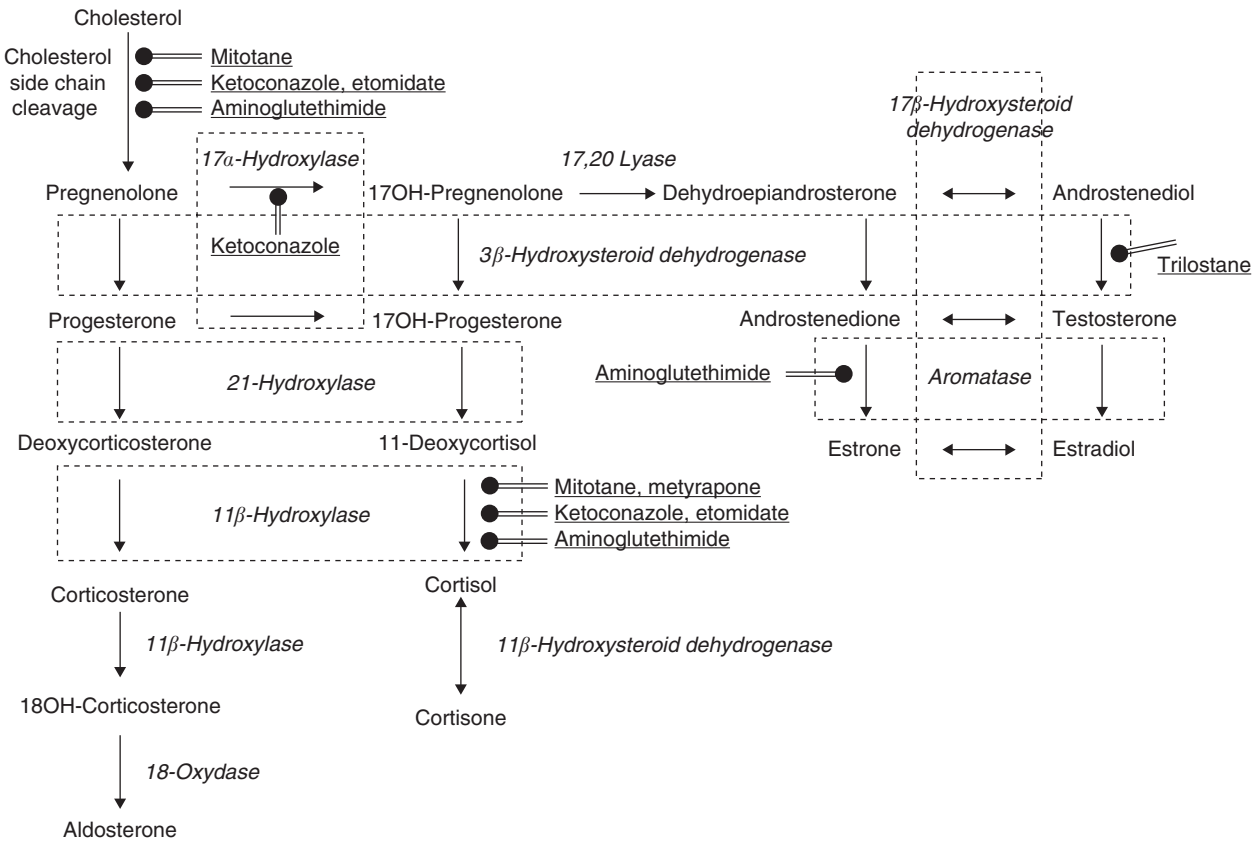

Figure 2. Adrenal steroidogenesis and steroid synthesis inhibitors. Enzymes involved in adrenal steroid synthesis are shown in italic, drugs are underlined. Filled circles indicate blockade by a given compound.

patients unable to take oral medication – and its hypnotic effect. Indeed, etomidate has been administered to sedate patients with severe psychosis [20,21].

Dosage of etomidate ranges from 1 – 3 mg/h, corresponding to the non-hypnotic 0.03 – 0.06 mg/kg/h range, to higher, sedative doses (0.2 – 0.3 mg/kg/h), which induce complete adrenal unresponsiveness to ACTH [22]. Some authors initiated treatment with the higher dose then proceeded with lower doses [19,23], whereas others favored the opposite sequence [24,25]. Steroid replacement therapy has to be instituted as soon as cortisol levels fall below the normal range in order to prevent an adrenal crisis. The effect of etomidate is self-limited and cortisol levels rise to pretreatment values within 24 h of drug withdrawal after short-term administration [26], whereas prolonged treatment may induce a more lasting adrenal suppression [23]. Most studies report short-term treatment with etomidate (4 – 12 days) in order to contain severe symptoms and reduce surgical risks [20,24,25]. Of interest, etomidate was administered for > 5 months to an intubated patient [23] and even, briefly, to a child with Cushing's disease [25]. In summary, intravenous etomidate may be useful for severely ill patients or patients requiring parenteral drug administration. As only isolated studies report on its long-term use, other, more manageable drugs should be reinstated as soon as feasible.

3.1.4 *Mitotane*

In addition to interfering with cortisol synthesis, mitotane (i.e., *o,p*'DDD) destroys adrenal cells and thus is usually used for treatment of adrenal cancer rather than benign Cushing's syndrome. A most recent multi-center study demonstrated that adjuvant mitotane treatment at low doses (1 – 3 g/day) prolonged recurrence-free survival up to threefold in patients with adrenal carcinoma [27]. Not all patients respond, however, possibly owing to the need for mitochondrial activation of *o,p*'DDD [28] and to tumor secretory status. Indeed, non-cortisol-secreting adrenal carcinomas appear less favorably affected by mitotane than cortisol-secreting tumors [29]. Mitotane has occasionally been used also in patients with ectopic ACTH secretion, Cushing's disease and adrenal nodular hyperplasia [30,31], in one case for up to 18 years [32]. Side effects, for example gastro-intestinal and neurological complaints, hypercholesterolaemia, accumulation in adipose tissue, unpredictability of individual responses and the need for steroid replacement therapy mandate handling of mitotane by expert centers. Of note,

severe pancytopenia and long QT syndrome have recently been reported in patients on mitotane [30,33].

3.1.5 Other adrenal blocking agents

Aminoglutethimide and trilostane warrant just a brief mention. These two adrenal synthesis inhibitors have been used in the past in a few cases [10], alone or together with other adrenal blocking agents. The risk of adrenal insufficiency is high and side effects may mar the efficacy of these drugs, thus their use is limited.

3.2 Glucocorticoid receptor blockers

The progesterone and glucocorticoid receptor antagonist mifepristone (RU486) was proposed in the 1980s for patients with Cushing's syndrome as blockade of the glucocorticoid receptor appeared a rational approach to treatment of hypercortisolism. However, the theoretical risk of adrenal insufficiency hampered its use and the drug never underwent formal clinical trials. Indeed, a recent paper reviews its use and found only 18 patients, mostly with ectopic ACTH secretion or adrenal carcinoma [34]. Clinical improvement was reported in most, although symptoms of adrenal insufficiency, for example nausea, hypoglycemia, hypotension and even adrenal crisis, developed in some [35]. Expert monitoring of patients treated with RU486 is necessary given its long half-life and the absence of specific markers of peripheral glucocorticoid activity. On balance, this drug awaits prospective clinical trials for its full efficacy and/or side effects to be established.

3.3 Neurotransmitters and neuromodulators

3.3.1 Serotonin antagonists

Serotonin antagonists have been used in the past to restrain tumoral ACTH secretion with mostly anecdotal results. Indeed, although *in vitro* evidence indicates a direct inhibitory action of cyproheptadine, a competitive serotonin and histamine receptor blocker, on ACTH secretion by human corticotroph cells [36,37], only individual cases of long-term remission on cyproheptadine have been reported [38,39], in some case persisting even after drug withdrawal [40]. Newer, more selective and long-acting serotonin receptor antagonists have been developed, but efficacy in Cushing's disease remains inconsistent. Indeed, ketanserin and ritanserin induced stable improvement in only 3 out of 11 patients with Cushing's disease [41]. A unique use of serotonin antagonists could be inhibition of excess cortisol secretion in patients with adrenal hyperplasia expressing ectopic serotonin receptors [9], but selective antagonists for serotonin receptor subtypes 4 and 7, the most frequently expressed receptors [42,43], have yet to be tested in this condition.

3.3.2 GABAergic compounds

Evidence on the possible efficacy of sodium valproate, an enhancer of GABAergic neurotransmission and inhibitor of ACTH secretion by rat anterior pituitary cultures [44], in Cushing's disease dates back several years and is limited to isolated reports [45]. Beneficial effects have also been reported in patients treated with sodium valproate and steroid synthesis blocking agents, but efficacy is by and large limited [46].

3.3.3 Dopamine agonists

Dopamine is a direct inhibitor of ACTH secretion by human corticotroph cells [37] and, indeed, several studies have investigated the therapeutic potential of bromocriptine, a preferential dopamine receptor 2 agonist, in Cushing's disease. However, results were disappointing and < 10% of patients achieved a reduction in ACTH and cortisol secretion [47]. Uninspiring results were also obtained with the depot bromocriptine formulation [48] and escape frequently occurred even in patients in whom bromocriptine appeared to be clinically effective [49]. The drug has not been completely abandoned, however, as beneficial effects on ACTH and cortisol secretion as well as amelioration of oculomotor movements have been reported just recently [50]. Further, recent studies with cabergoline, a long-acting dopamine receptor 2 agonist, yielded promising results, with a marked decrease in ACTH and cortisol observed in 6 out of 10 patients with Cushing's disease on 1 – 2 mg/week cabergoline for 3 months [51]. Responsiveness to cabergoline was associated with dopamine receptor 2 expression and binding in the tumor, which occurred in 15 out of 20 tumoral specimens [51]. Subsequent studies with higher cabergoline doses (up to 7 mg/week) or for longer periods of time (up to 1 year) have been presented in poster format, and responsiveness to cabergoline ranges from 40 to 70% [52,53]. Treatment with cabergoline also led to shrinkage of an ACTH-secreting pituitary macroadenoma [54,55], in keeping with the pro-apoptotic effect of dopamine agonists on tumoral corticotrophs [56] and the ability of these compounds to alter blood flow within the tumor [57]. Dopamine agonists also inhibit proliferation and ACTH synthesis by small cell lung cancer cell lines [58,59], possibly again by means of the type 2 receptor [60], which has led to their use in patients with ectopic ACTH secretion. Treatment with either bromocriptine [61,62] or cabergoline [60] yielded mostly transitory benefits, although one patient maintained normal adrenocortical function on bromocriptine for 4 years [62]. Except for individual cases of peculiar sensitivity to dopamine agonists, however, escape from the suppressive effect is common and limits the long-term usefulness of these drugs to a few, responding patients. A cautionary note has arisen from recent reports on increased cardiac valve disease in patients with Parkinson's disease on cabergoline [63]. It should be noted, however, that Parkinson's disease requires considerably higher doses than any attempted so far in Cushing's disease (on average 3.6 mg/day) and that no patient treated with a total cabergoline dose < 1 g was found to have significant valve regurgitation [64]. According to a rough estimate, therefore, an increased risk of cardiac

valve disease would occur in patients taking 1 mg cabergoline daily for at least 3 years; long-term risk-assessment studies on cabergoline administration to patients with Cushing's disease are needed should the drug prove useful at high dose regimens.

3.3.4 Somatostatin and somatostatin analogues

Somatostatin, a brain-gut peptide that inhibits the secretion of several hormones, most notably growth hormone (GH) and insulin, has in the past been tested as a potential inhibitor of ACTH secretion, with variable results. Solid experimental evidence had accrued in the 1980 – 90s demonstrating that somatostatin inhibits ACTH secretion [65,66], and these results have been substantiated by recent findings on somatostatin or somatostatin receptor knockout mice displaying increased pituitary synthesis and secretion of ACTH [67,68]. Clinical studies, however, failed to demonstrate efficacy of somatostatin or octreotide, the only available somatostatin analogue at the time, in patients with Cushings's disease [69,70]. Detailed *in vitro* studies revealed that octreotide reduces ACTH secretion by tumoral corticotropes but that this effect is abolished by co-incubation with glucocorticoids, thus explaining the discrepancy between *in vivo* and *in vitro* findings in patients with Cushing's disease [70-72]. Accordingly, a reduction in ACTH levels was observed in adrenalectomized patients with rapidly growing pituitary corticotrope tumors, that is, Nelson's syndrome, treated with octreotide [69]. Somatostatin and octreotide both proved capable of inhibiting ACTH secretion by ectopic ACTH-secreting tumors [73,74], in keeping with the inhibitory action of somatostatin in neuroendocrine-secreting tumors. Long-term octreotide formulation as well as lanreotide, a somatostatin receptor 2 agonist with longer half-life, have also been administered with success to patients with ectopic ACTH secretion [75,76].

The development of newer, differently selective somatostatin receptor agonists over the last few years has revived interest in this issue and, indeed, yielded promising results. One of the first new somatostatin receptor agonists, SOM230 or pasireotide, interacts with all somatostatin receptor subtypes except subtype 4 and shows the highest affinity for receptor type 5 [77]. *In vitro* studies have shown that SOM230 inhibits ACTH release and cell proliferation in human corticotroph tumors [71,78] and that this effect is mediated by the somatostatin type 5 receptor. This receptor subtype is the most abundant in corticotroph tumors [71] and, unlike receptor type 2, is not suppressed by glucocorticoids [71,72]. These findings may explain the lack of efficacy of octreotide in Cushing's disease, as it acts preferentially on somatostatin type 2 receptors. On the other hand, recent experiments on murine tumoral corticotrophs revealed a functional interaction between somatostatin receptors type 5 and type 2 [79]. Further experimental evidence emphasized this concept as SOM230 inhibited basal and CRH-stimulated ACTH release with greater potency than BIM23268, a selective type 5 somatostatin receptor agonist [78]. Further, SOM230 prevented the increase in pituitary mitotic activity induced by adrenalectomy [80] and was far more potent than octreotide in blunting *in vivo* CRH-stimulated ACTH and corticosterone secretion [81]. Studies in other pituitary tumors revealed that SOM230 also affects vascular endothelial growth factor secretion [82], MAPK pathway [83], and can induce tumor regression in transgenic mice bearing mammosomatotroph tumors [84]. Clinical studies are as yet in Phase II, but appear promising. Indeed, preliminary data on 27 patients with Cushing's disease treated with 600 μg pasireotide twice a day for 2 weeks showed reductions in UFC in 9 patients and normalization in 4 [85].

Other somatostatin analogues targeted to single somatostatin receptor subtypes are being developed and await testing on corticotroph adenomas. Agonists such as BIM23268, which is selective for somatostatin receptor 5, might prove extremely interesting in view of the prominent role of this receptor subtype in controlling ACTH release [68,72]. In alternative, antitumor somatostatin analogues such as TT-232, which are capable of controlling intracellular proliferative signals and inducing apoptosis, are promising candidates for neuroendocrine malignancies [86].

3.3.5 Somatostatin/dopamine receptor agonist chimeras

A new avenue for research is somatostatin–dopamine agonist chimeras that unite the two inhibitory mechanisms discussed above. Only limited *in vitro* data are available for these agents and, to the best of the authors' knowledge, no study on actively secreting corticotroph tumors has been published so far. A somatostatin–dopamine chimera acting on the somatostatin type 2 receptor as well as the dopamine type 2 receptor has been tested in two silent corticotroph tumors and reduced cell viability in one but not the other specimen [87]. In human GH or prolactin-secreting tumors, the chimeric ligand appeared more potent than either somatostatin or dopamine analogues alone [88], in keeping with the enhanced functional activity of somatostatin–dopamine receptor heterodimers [89]. No patient has yet been tested with these chimeras, but proof of concept can be gained by the patient with an atypical lung carcinoid causing Cushing's syndrome in whom combined treatment with lanreotide and cabergoline proved superior to either drug alone [90].

3.3.6 Somatostatin radiolabeled therapy

One alternative approach to ectopic Cushing's syndrome or huge pituitary corticotroph adenomas is peptide receptor radionuclide therapy. Somatostatin analogues labeled with β-emitting isotopes, such as ^{90}Y or ^{177}Lu, and infused intravenously can deliver high dose radiation to tumor cells by means of endocytosis of the somatostatin analogue by its receptor [91]. Clinical trials with ^{90}Y-DOTA-Tyr^3 octreotide (^{90}Y-DOTATOC) yielded favorable results in patients with

inoperable or disseminated neuroendocrine tumors, as did those with ^{177}Lu-DOTA-Tyr^{3} octreotate (^{177}Lu-DOTATATE), a newer somatostatin analogue with higher affinity for the somatostatin type 2 receptor [92]. Most recently, peptide receptor radionuclide therapy with both analogues was attempted in a patient with ectopic ACTH secretion due to a pancreatic, metastasized neuroendocrine tumor resulting in long-term regression of hormonal hypersecretion and clinical features and shrinkage of tumor and metastases [93].

3.4 New compounds

In the past few years, experimental studies have identified two new classes of agents for treatment of Cushing's disease, namely retinoic acid and peroxisome proliferator-activated receptor (PPAR) gamma agonists. Only PPAR-γ agonists have been tested so far in patients with variable results and new compounds remain an active venue of research.

3.4.1 PPAR-γ agonists

PPAR-γ is part of a nuclear receptor family involved in several actions, including adipose tissue differentiation, lipid and glucose metabolism, inflammation and tumorigenesis. Its interest in Cushing's disease arose from the breakthrough study at Cedars-Sinai showing that thiazolidinediones (i.e., exogenous PPAR-γ ligands) exert an antiproliferative and pro-apoptotic effect on murine tumoral corticotrophs [94]. Indeed, the development of tumor implants was prevented in mice treated with the thiazolidinedione rosiglitazone [94]. This evidence led to clinical trials with rosiglitazone or its sister compound, pioglitazone, but results in humans were less striking than in mice. In fact > 30 patients have been tested with either compound and significant decreases in UFC, cortisol or ACTH have been registered only in a minority of patients [95-100]. The timing of pituitary–adrenal responsiveness to PPAR-γ agonists is also individualized, with some patients presenting a decrease in UFC within 2 – 3 months of treatment [95,97] and others developing later responses [98,99]. Escape from the suppressive effect has also been reported [98]. On balance, clinical results were disappointing compared with the expectations stirred by animal studies, possibly a consequence of the different proliferative potential of murine and human tumoral corticotrophs and the low expression PPAR-γ receptors in the nucleus of human pituitary cells [101]. Thiazolidinediones might also exert their antiproliferative action independently of the PPAR-γ receptor [101]. Rosiglitazone has also been administered to a few patients with expanding pituitary tumors (i.e., Nelson's syndrome and macroadenomas), again without significant decreases in ACTH secretion [97,102,103]. Of note, some patients on rosiglitazone reported clinical improvement in addition to amelioration of insulin sensitivity [95,96], thus PPAR-γ agonists may prove useful as adjuvant therapy in some cases. Overall, beneficial effects of PPAR-γ agonists appear limited so far.

3.4.2 Retinoic acid

The potential efficacy of retinoic acid in Cushing's disease is even greater than that of PPAR-γ agonists, as it has been shown to prevent synthesis and secretion of ACTH by both human and murine tumoral corticotrophs, in addition to its antiproliferative effect on these same cells [104,105]. The use of this drug appears most advantageous as these effects were observed only in tumoral corticotrophs; indeed, normal pituitary corticotrophs present a pattern of transcription factors that does not allow retinoic acid to inhibit ACTH synthesis/secretion [104]. So far, retinoic acid has been administered only to dogs with Cushing's disease, with remarkable results, including reduction in ACTH and urinary cortisol concentrations, shrinkage of the pituitary tumor and improvement of clinical signs and survival times [106]. Both retinoic acid receptor isoforms are expressed in ACTH-secreting tumors [107], thus the rationale for attempting retinoic acid administration in human Cushing's disease is sound.

4. Conclusion

Nearly 100 years have passed since the first description of Cushing's syndrome by Harvey Cushing but therapeutic management of his namesake syndrome is still not fully satisfactory. In fact, only a few viable medical agents are available at present for patients who fail at first choice treatment, that is, surgery, or relapse. The mainstay remain steroidogenesis inhibitors, chiefly ketoconazole, but the impetus provided by studies in the past few years will hopefully pave the way to better and more specific treatments.

5. Expert opinion

Treatment of Cushing's syndrome, particularly medical therapy, continues to challenge even the most skilled endocrinologist. The advances that occurred in the recent past, however, justify a more optimistic outlook into the future; indeed, the intense interactions between endocrine centers all over the world now enables a more judicious choice among available therapeutic options. Accordingly, surgery, radiation and medical therapy are being used with increasingly better results.

Although steroid synthesis inhibitors, foremost ketoconazole, continue to be the more widely used pharmacological tool for Cushing's syndrome, new, selectively targeted compounds are under investigation and are yielding encouraging results. More potent and at the same time more manageable molecules for a temporary or permanent chemical adrenalectomy will become available, to be used chiefly in primary adrenal hypercortisolism. On the other hand, the possibility of blocking ACTH secretion in patients with Cushing's disease and, hopefully, also in patients with neuroendocrine ACTH-secreting tumors, is rapidly approaching. Newer dopamine receptor agonists at high doses, such as 7 mg/week

cabergoline, have been tested in small groups of patients with Cushing's disease and achieved reduction/normalization in UFC secretion in 40 – 70% of patients. Even long-lasting remissions while on cabergoline have been reported. Along the same line, recently developed somatostatin receptor ligands are proving beneficial in patients with Cushing's disease. One such compound, SOM230 or pasireotide, a somatostatin multireceptor ligand, is now in a Phase II multicenter international study and appears to reduce/normalize UFC in up to 50% of patients with Cushing's disease. The development of chimeric dopamine–somatostatin receptor ligands is an obvious progression that is already underway. Somatostatin ligands are also ideal candidates for peptide receptor radionuclide therapy and isotopes can thus deliver concentrated radioactivity to neuroendocrine cells, both outside and within the pituitary. The use of PPAR-γ agonists in Cushing's disease has strong experimental support and, although results obtained so far with rosiglitazone and pioglitazone are not fully satisfactory, further studies could provide more effective molecules. Similar considerations apply to retinoic acid, which has yielded spectacular results in animals but has not been investigated as yet in man.

In summary, medical therapy together with surgery and radiation therapy have significantly improved the outcome for patients with Cushing's syndrome. The near future will probably see further progress in the tools available to cure this severe endocrine disorder.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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