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Review Article

Pharmacological Management of Cushing's Disease

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Abstract

The role of pharmacological management of Cushing's disease is dual, to prepare patients before any surgical intervention and to control untreated hypercortisolemia. The latter is mainly relevant in cases of persistent disease due to surgical failure, while waiting for the delayed effect of radiotherapy or as treatment in patients who are poor candidates for surgery. Drugs targeting the adrenocorticotropin-secreting pituitary adenoma include the somatostatin analog pasireotide and the dopamine agonist cabergoline, even though their effects are not well established as in growth hormone secreting adenomas or prolactinomas. Adrenal-specific therapy includes inhibitors of adrenal steroidogenesis and glucocorticoid antagonists. Metyrapone and ketoconazole help to control hypercortisolaemic states rapidly; osilodrostat and levoketoconazole have evolved as new alternatives due to their higher efficacy and less incidence of adverse effects. Mitotane may be useful in selective cases, in lower doses than those used in adrenocortical carcinoma, while etomidate is a life-saving treatment in an emergency setting. The glucocorticoid antagonist mifepristone is effective for rapid control of hypercortisolemia, but the risk of hypoadrenalism is not always acceptable. A combined treatment appears safer, more rapid and more effective to control hypercortisolemia than each drug alone.

Novel treatments include the use of retinoic acid, temozolomide, doxazocin, gefinitib, bevacizumab, seliciclib, IRC-274. The increasing clinical experience and understanding of the molecular pathways may help to achieve pharmacological therapy without the need for a surgical approach.

ABBREVIATIONS

ACC: Adrenocortical Carcinoma; ACTH: Adrenocortitropin; AE: Adverse Effect, BP: Blood Pressure; CD: Cushing's Disease; CDK: Cyclin-Dependent Kinases; CHA: Carbohydrate Metabolism Abnormalities; CS: Cushing's Syndrome; DA: Dopamine Agonist; DR: Dopamine Receptor; GLP-1: Glucagon-Like Peptide 1; GR: Glucocorticoid Receptor; HPA: Hypothalamic-Pituitary-Axis; LAR: Long-Acting-Release; LDS: Low-Dose Dexamethasone Suppression Test; MC2: Melanocortin-2; MC2R: Melanocortin-2 Receptor; MGMT: O6-Methylguanine-DNA Methyltransferase; MNS: Midnight Serum Cortisol; MRI: Magnetic Resonance Imaging; POMC: Proopiomelanocortin; SA: Somatostatin Analogue; SCC: Side-Chain Cleavage Complex; SSTR: Somatostatin Receptor; TSS: Transsphenoidal Surgery; UFC: Urine Free Cortisol; ULN: Upper Limit Of Normal

INTRODUCTION

Cushing's disease (CD), defined as the presence of an adrenocortitropin (ACTH)-secreting pituitary adenoma, represents the most frequent cause of endogenous hypercortisolaemia [1]. As the majority of these tumors are microadenomas (size <10 mm in diameter), first-line treatment for CD is the surgical removal of the adenoma, which, in cases of surgical failure, may be followed by radiotherapy or bilateral adrenalectomy (BA); however, the need for adrenalectomy is not currently a common practice. Medical treatment for CD is an alternative or even preferable approach in patients who are not candidate for surgery because of co-morbidities. Medical therapy is also employed after radiotherapy or radiosurgery while awaiting their delayed effects, or before surgery to shrink the risk of infection, poor healing, and cardio-metabolic consequences (along with other measures such as prophylactic useof heparin) [2,3].

Even though medical management is not considered as first line treatment in CD compared to other pituitary adenomas, several agents that target the ACTH-secreting pituitary adenoma directly, have been introduced recently. Corticotrophs, express high levels of somatostatin (SSTR) 5 and dopamine receptor (DR) 2 [4]. Pharmacotherapy targets these receptors using SSTR ligands and dopamine agonists (DA), respectively, to decrease ACTH production by corticotroph adenomas. Other novel drugs target corticotrophs secretion control along with adrenal specific therapy. The present review summarizes currently available

drugs for the treatment of CD, their mode of action and side effect profile.

Drugs targeting ACTH-secreting adenoma

Somatostatin analogues (SAs): SAs use is based on SSTR inhibition [5]. Most corticotroph adenomas (> 85%) express SSTR2, SSTR5 and to a lesser extent SSTR1 (63%) mRNA [6]. The surface membrane density of SSTR varies with the degree of hypercorticosolemia, particularly for SSTR2, while SSTR5 expression appears to be relatively unaffected [7-9]. Therefore, in patients with active CD, SSTR5 is predominantly expressed compared to SSTR2 [9]. It was documented that after restoration of eucortisolemia, SSTR2 expression recovers, becoming similarly abundant to SSTR5, thus improving treatment responsiveness to long acting SAs [8,10-14]. In line with thisfinding, octreotide, a predominantly SSTR2-selective ligand with moderate affinity for SSTR5, has been shown to be virtually ineffective in controlling hypercortisolemia in patients with CD [8,10,11,15].

Pasireotide or SOM-230: A multi-ligand SAs with high binding affinity to SSTR5 and 1, 2 and 3 subtypes were approved for the treatment of patients with CD in whom surgery has failed or is not possible The functional activity of pasireotide compared to octreotide has been found to be 30-fold, 11-fold and 158-fold higher on SSTR1, 3 and 5 respectively, and approximately 7-fold lower on SSTR2, being more potent compared to octreotide in inhibiting basal ACTH release [16]. In a phase II, open-label, single-arm, multicentre pilot study, 29 CD patients self-administered subcutaneous pasireotide 600mcg twice daily for 15 days obtaining urine free cortisol (UFC) level reduction in 75.8% and normalization in 17.2% of cases respectively [17]. A subsequent double blinded, randomized, multicenter phase III trial with pasireotide 600–900mcg twice daily, revealed UFC reduction in most of 162 CD patients treated and normalization in a further 25% of them. Responders were identified within 2 months of treatment and UFC level normalization was higher in patients with mild CD (UFC up to twice upper limit of normal) [18]. Late-night salivary cortisol was also measured in 93 patients, and normalized in 37% and 19% of patients at 6 and 12 months respectively [19]. Approximately 48% of patients with complete UFC normalization at 12 months remained controlled at 24 months [20]. Discontinuation rate was high due to unsatisfactory therapeutic effect (32.7%), development of adverse effects (AEs) (22.2%), consent withdrawal (18.5%) and administrative problems (9.9%). Significant improvement in clinical signs and symptoms was seen from 12 to 60 months of treatment, suggesting that this agent is appropriate for long-term treatment [21,22]. In 75 patients with a measurable lesion on magnetic resonance imaging (MRI) who were treated with900mcg of pasireotide, mean tumour volume decreased by 44% [18]. In 8 CD patients treated with pasireotide 600-1200μg twice daily from 6 up to 24 months, significant tumour shrinkage (defined by a reduction > 25% of size) was diagnosed after at least 12 months of treatment with tumour mass disappearance in one case [23]. It was therefore suggested that pasireotide could be considered as a neo-adjuvant treatment before surgery, since tumour shrinkage was seen in corticotroph macroadenomas on *de novo* treatment with pasireotide [24]. Of note 73% of patients treated with pasireotide, reported more frequent and more severe hyperglycemia and 6% of them discontinued the treatment; other AEs were due to SAs (gastrointestinal, including biliary sludge and gallstones) [2,18]. Pasireotide-induced hyperglycemia in healthy volunteers is mediated by incretin hormone, glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP) reduction followed by decline of insulin secretion; metformin and dipeptidyl peptidase-4 (DPP4) inhibitors or GLP-1 agonists may represent an appropriate treatment, while insulin may be required in more severe cases of glucose intolerance [24,25]. Clinicians should correct hypokalemia and hypomagnesemia before initiating pasireotide and test baseline liver function tests, thyroid function, IGF-1, fasting glucose and HbA1c. In addition, gallbladder ultrasound to exclude cholocystopathy and electrocardiograms for corrected QT interval prolongation or bradycardia should be performed. Treatment should be administered after (not before) meals and follow dietary recommendations for diabetes [2]. An intramuscular long-acting-release (LAR) formulation of pasireotide approved for the treatment of acromegaly is now being evaluated for use in CD.

Pasireotide LAR: It has previously been reported to be effective in reducing ACTH and tumour volume in a patient with Nelson's syndrome and aggressive corticotroph tumour growth [26]. In a double-blind randomized controlled trial phase III, 150 patients with persistent, recurrent or de novo CD were treated with pasireotide LAR 10 or 30 mg monthly, for a duration of 7 months; UFC normalization was observed in 40%, with a 48% median decrease of UFC in patients treated with pasireotide LAR 10 or 30 mg monthly for a duration of 7 months. Hyperglycemia-related AEs were noted in 68% and 80% of patients in the 10 and 30 mg groups, respectively, leading to treatment discontinuation in only 5 patients [27].

Somatropim (DG3173): A novel multi-ligand SA that selectively binds to SSTR2, SSTR4, and SSTR5, without potent effect on insulin secretion, has been tested in patients with acromegaly but has not been evaluated on CD yet [28]. Dopamine receptor 2 has a heterogeneous expression in 89% of all types of pituitary tumours and it has also been detected in 69%-75% of silent or functioning ACTH-secreting pituitary tumours [29,30]. Dopaminergic modulation of ACTH secretion has been suggested to occur via regulation of hypothalamic corticotrophin releasing hormone (CRH) release in addition to direct inhibition of ACTH secretion by the corticotrophs [31,32]. In CD, the DA bromocriptine has shown limited therapeutic potential and in the past, it has only been used in patients with cyclical CD [24,30,33].

Cabergoline: An ergot-derived DA with high affinity for DR2, has been investigated in patients without optimal surgical outcome [9], since *in vitro* studies have shown that it inhibits ACTH secretion from DR2-positive cells [30]. In 20 patients with initial response up to 75% (partial response defined as a decrease greater than 25% complete normalization as full response) [34], 40% still had a sustained response over a 2-year period with median cabergoline dosage of 3,5mg/week [34]. Assessing cabergoline effectiveness in patients with CD by midnight serum cortisol (MNS) alone or low-dose dexamethasone suppression serum cortisol (LDS) alone or their combination it was found improvement in a range 17% and 25% [35]. A retrospective study including a cohort of 30 CD patients treated with cabergoline (initial dose of 0.5-1mg/week, increased up to 6mg/week), reported a complete response in 37% of them. Additionally, 30% of them, under a mean dose of 2.1mg/week, remained asymptomatic in a 3 years follow up period. On the other hand,

patients who did not respond to carbegoline, were treated with a mean dose of 2mg/week (range 1-4.5mg/week) for an average period of 4months (range 1-9months), and it is possible that the maximal inhibitory effect might have been underestimated [36]. Approximately 25% of patients may develop a cabergoline escape phenomenon at 2-5years. Tumour volume decreased or remained stable in the small number of reported patients with visible adenomas [34,36], but no consistent dose-dependent reduction in cortisol levels was seen in a short-term prospective study of 20 patients treated with a median dose of cabergoline of 5mg/week [37]. Adverse effects included nausea, dizziness, and asthenia [2,34]. Potential concerns include the long-term safety of these drugs as due to the activation of valvular fibroblasts through serotonin receptor 2B [38].

Retinoic acid: It is a nuclear receptor ligand with inhibitory effect on corticotroph tumour growth, POMC transcription, plasma ACTH, and corticosterone secretion from ACTH-secreting pituitary tumours in animal models and *in vitro* experiments [39,40]. Retinoic acid increased caspase-3-activity-induced cell death, while its antiproliferative action has been shown to be mediated through bone morphogenetic protein 4 (BMP4), a member of the transforming growth factor beta (TGF-β) super family that plays a central role during pituitary organogenesis and transcription [41]. Additional beneficial effects include reduction of adrenal hyperplasia by direct inhibition of adrenal cell proliferation, reversal of skin atrophy and immunostimulation [42]. Recently, in a longitudinal, non-controlled, non-randomized, multicenter study, 7 CD patients were treated with 10mg/day retinoic acid, progressively increased to 80mg/day. After 6-12 months of treatment, 43% demonstrated normal UFC levels with only mild AEs. Moreover marked decrease in UFC levels was observed in 71% of patients with mean UFC levels being 22%-73% lower of baseline values. Furthermore, plasma ACTH levels started to decrease after the first month of treatment, but subsequently returned to pre-treatment levels. Clinical signs of hypercortisolism were also ameliorated [43]. A recent open-label clinical trial demonstrated that 20-80 mg/day of the 13-cis isomer of retinoic acid, isotretinoin, resulted in UFC reductions of up to 52% and normalization in 25% of 16 patients with CD at 12 months [44]. More than 40% of patients reported mild and reversible AEs (xerophthalmia and arthralgias).

Temozolomide: It is an orally administrated second-generation alkylating chemotherapeutic drug that methylates DNA at the O6 position of guanine, causing a mismatch with thymine during the next DNA replication cycle, leading to cell apoptosis [45]. Drug efficacy relies on O6-methylguanine-DNA methyltransferase (MGMT) enzyme activity, since MGMT reverses alkylation. After treatment with temozolomide, tumours become soft and friable, and display better differentiation, less mitoses, and a lower Ki-67 index [46]. Temozolomide has been used in cases of aggressive corticotroph pituitary adenomas or carcinomas refractory to surgery or pituitary irradiation with promising results [47,48]. In a patient with a pituitary carcinoma, the combination of pasireotide with temozolomide administered over 12 months, was associated with sustained control of tumour growth and ACTH secretion, indicating that such anoption may be a promising for aggressive pituitary tumours [49]. Temozolomide was well tolerated and few severe AEs have been described but care should be given for the bone marrow suppression [50].

Adrenal-specific therapy

Inhibitors of cortisol secretion: As previously mentioned, an important step to control ACTH induced hypercortisolemia is the use of drugs aiming at adrenal glucocorticoid secretion. These compounds decrease cortisol levels by direct inhibition of steroidogenesis at one or more enzymatic steps, not affecting the underlying tumour and without restoring normal hypothalamic-pituitary-axis (HPA) secretory dynamics. All these medications require dose escalation of the initial low dose and frequent monitoring, in order to achieve an acceptable clinical and biochemical profile and minimize their side effects. Occasionally adrenal steroidogenesis inhibition can be partial or complete; to overcome this limitation, a "block-and-replacement" scheme has been used: a complete blockade of zona fasciculate steroidogenesis is achieved with concomitant hydrocortisone replacement. In either case, patients should be well informed about adrenal insufficiency or the recurrence of hypercortisolism symptoms. Notably, since corticotroph tumours have a higher than normal set-point for cortisol negative feedback on ACTH suppression, ACTH secretion may increase in parallel with the fall of cortisol levels necessitating an increase of the dose of these drugs over time .

Metyrapone: It displays a rapid onset and high effect of action, by blocking 11β-hydroxylase (CYP11B1) that converts 11-deoxycortisol to cortisol in the adrenal cortex. Additionally, itinhibits17α-(CYP17A1), 18- (CYP11B2) and 19-hydroxylase [24,45,51], obtaining adequate control of cortisol levels in short- and long-term [52]. Its action is usually obvious within hours, after an initial daily dose of 0.5-1g (starting with 250mg 4-times/day). Treatment should be adjusted in 3-4 divided doses daily, increased every few days to a maximal daily dose of 6-8g [24,51]. In the largest recent multicentre study of 195 patients with CS, biochemical control was achieved in 83% of patients with monotherapy and in 76% of those with combination treatment (mainly ketoconazole or mitotane). In 164 patients on monotherapy, 55% had a normal cortisol day curve, and 43% of patients had normal UFC levels respectively, at the last review. Longer-term data (mean 18 months) in 38 patients showed biochemical eucortisolism in 72% of them. In 23 patients with CD not previously irradiated, biochemical control by UFC assessment was achieved in 57% and clinical improvement was obtained in 46% of patients [53]. Its strong cortisol-lowering effect results in loss of its negative feedback on ACTH and a consequently rise of ACTH levels leading to increase of androgenic precursors resulting in acne and hirsutism, a common cause of treatment discontinuation [51,54]. Hypertension, hypokalaemia and oedema are caused by an increment of mineralocorticoid precursors that is counteracted by the parallel cortisol drop [53]. Dizziness and gastrointestinal upset (minimized when the medication is taken with food or milk), may be caused by adrenocortical insufficiency [45,51,55]. This medication has also been given in pregnancy without serious adverse outcomes in either the mother or the fetus [2,56]. It is important to note that 11-deoxycortisol is increased and it may cross-react with many cortisol assays and the risk for unrecognised hypocortisolemia is high, except when liquid chromatography tandem mass spectrometry (LC-MS/MS) is used [57].

Osilodrostat (LCI699): It is an oral potent inhibitor of human 11β-hydroxylase (3-fold more potent and with a longer

half-life compared to metyrapone) and aldosterone synthase, which are responsible for catalysing the final steps of cortisol and aldosterone biosynthesis, respectively, in the adrenal cortex [58]. In one proof-of-concept study of 12 patients with moderate-to-severe CD, an initial dose of 4mg/day osilodrostat was administered. The dose was escalated every 14days to 10, 20, 40, and 100mg/day twice daily. The results of the study were encouraging regarding the efficacy and safety of 10 weeks treatment. All patients achieved UFC levels within the upper limit of normal (ULN) or a > 50% decrease from baseline levels while 92% obtained normalization of UFC levels. Mean 11-deoxycortisol, 11-deoxycorticosterone, and ACTH levels increased during treatment and declined after discontinuation. Improvement was also noted in blood pressure (BP) levels [59]. In the extension phase study, 4 patients of the original cohort and 15 new patients with CD with UFC levels > 1.5 ULN were recruited. Patients received initially 4-10 mg/day of osilodrostat and doses were adjusted every 2 weeks to 10-60 mg/day until UFC levels normalized. UFC levels were normalized in 78.9% of patients at 22 weeks [60]. At 19 months mean UFC levels and 0800 morning serum cortisol levels were within the normal range with an overall response rate 93.8%, whereas no treatment escape phenomenon were observed. Improvement was also noted in body mass index [61]. Osilodrostat was generally well tolerated; most AEs were mild or moderate (fatigue, nausea, headache, diarrhea; in females, hirsutism and acne) while adrenal insufficiency and glucocorticoid withdrawal was reported in one-third of patients reflecting the potency of osilodrostat [59,60].

Ketoconazole: An imidazole, blocking cytochrome P450 enzyme acting at several sites, exerts its strongest effect on 17,20-lyase, and side-chain cleavage complex (P450scc, CYP11A1, 20,22 desmolase), 11β-hydroxylase, 17α-hydroxylase [45,51,62]. It has as lower onset of action than metyrapone, occurring over several days or possibly weeks. Moreover, its multi-target inhibition results in a reduction of androgen synthesis with favourable effects on hirsutism. Extra-adrenal actions have been reported since an acute *in vitro* decrease in basal and CRH-stimulated ACTH secretion by corticotroph tumour cells was obtained from two patients with Nelson's syndrome [63]. At high concentrations, it has been shown *in vitro* to act as an antagonist of the glucocorticoid receptor (GR) [64]. Treatment with ketoconazole is usually started at 400mg/day (divided in 2 doses) and increased every 3 or more days to a maximum dose of 1.2-1.6g/day in 3-4 divided doses. Because gastric acidity is necessary to metabolise this medication into its 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 [45,51]. Recently its efficacy and safety profile have been confirmed in a French retrospective multicenter (FReSKO) study. In this study, data from 200 patients with CD treated by ketoconazole monotherapy at doses of 200–1200mg daily for pre-operative, primary and secondary treatment were analysed. At last follow-up (mean 20.6 months), approximately half of the patients achieved normal UFC levels and an additional 26% had a ≥ 50% decrease, associated with clinical improvement. Escape from treatment however was demonstrated in 23% of those with an initial response [65]. Ketoconazole has a relatively mild spectrum of AEs: gastrointestinal symptoms, irregular menses, gynaecomastia, decreased libido and impotence, which are the main cause of treatment discontinuation in men, teratogenicity that contraindicates its use in pregnancy, its interactions with other medications because of the potent inhibitory effects on cytochrome P450 enzymes (particularly CYP3A4, CYP2C9, CYP1A2) [2,24,45,66]. An idiosyncratic hepatic dyscrasia occurs in about 1 in 15.000 cases, and this may very rarely be fatal [2,51,66,67]. In the FReSKO study, intolerance of the drug resulted in treatment cessation in approximately one-fifth of patients; however, this was generally reversible upon drug withdrawal; liver enzymes increasedup to 5-fold in 13.5% of patients while severe hepatotoxicity (> 5-fold elevation) was seen in 2.5% [65]. It is recommended that liver function should be closely monitored and dose reduction or discontinuation is advised when liver enzymes are more than 3-fold elevated. The FDA issued a black box warning in 2013, and the European Medicines Agency has restricted access to the agent to physicians specialized in treating CS [2].

Levo-ketoconazole: It is the single 2S, 4R enantiomer of ketoconazole, purified from racemic ketoconazole (2S, 4R and 2R, 4S, racemic mixture). It is currently considered an investigational new drug being 2 and 7 times more potent than ketoconazole in inhibiting 21-hydroxylase (CYP21), 17α-hydroxylase and 11β-hydroxylase. Moreover, it displays a better safety profile being 12 times less potent than ketoconazole in inhibiting CYP7A1, resulting in less interference with bile acid synthesis and metabolite elimination, and therefore is anticipated to exert less hepatoxicity [66]. In a phase I study, when administered to healthy subjects, levoketoconazole (400mg/day) reduced serum cortisol levels significantly by day 4, compared to placebo and ketoconazole; the drug was well tolerated; headache, back pain and nausea were the most frequently reported AEs [68]. A single-arm, open-label, dose titration study (clinicaltrials.gov; NCT01838551) is currently assessing its efficacy, safety, tolerability and pharmacokinetics, in patients with CS [68,69]. In the context of safety profile and metabolic effects of 14 days of treatment with levo-ketoconazole, a phase IIa multicenter, randomized, double-blind, placebo-controlled, parallel-group trial was performed in drug-naïve or metformin-treated patients with type 2 diabetes mellitus. Interestingly, a reduction of cholesterol and C-reactive protein was seen in this short-term observation [70].

Etomidate: It is an imidazole derivative which compared to ketoconazole, inhibits 11β-hydroxylase more potently, showing a similar inhibition of 17α-hydroxylase but a lesser effect on 17, 20-lyase [71]; in higher concentrations, it influences cholesterol scc complex [72] but also aldosterone synthase (CYP11B2). Because of its rapid action and intravenous administration, it can be used in an emergency clinical setting in severely ill patients or in cases when oral therapy is either not tolerated or not feasible. It has been used successfully in cases of glucocorticoid-induced psychosis or respiratory failure, and has also been administered in children [73-75]. The recently published guidelines suggest, a loading dose of 3-5mg to be followed by a continuous infusion of 0.03-0.10mg/kg/h (2.5-3.0mg/hr) with dose titration if optimal cortisol levels are obtained; a maximum dose of up to 5mg/hr in selected cases has been used [2,76,77]. It is recommended to titrate the infusion rate to achieve a stable serum cortisol level between 280-560nmol/L in physiologically stressed patients or to 150-300nmol/l in unstressed patient; if complete blockade is desired, a 'block and replacement scheme' with hydrocortisone

infusion may be used to prevent adrenal insufficiency after 24hrs of etomidate infusion [2,77]. Monitoring of serum cortisol levels (every 4-6hrs) is necessary to achieve the desired blockade and to prevent hypoadrenalism. The recent guidelines for the treatment of CS recommend the management to take place always in an Intensive Care Unit (ICU) setting for adequate monitoring [2]. Care should be taken to avoid excessive sedation that may be apparent in higher doses, and adjustments should be made with regards to renal failure and stressed situations such as sepsis [77].

Fluconazole: An antifungal azole derivative, inhibits 11β-hydroxylase and 17α-hydroxylase being less toxic than ketoconazole, which can be administered in intravenous or oral form. Fluconazole at a dose of 100mg twice daily successfully controlled UFC levels in 2 patients [78].

Mitotane O,p'DDD: 1-(o-Chlorophenyl)-1-(p-chlorophenyl)-2,2-dichloroethane), inhibits steroidogenesis acting on cytochrome P450 enzymes CYP11A1, 11β-hydroxylase, and 18-hydroxylase, and non-P450 enzymes (3β-hydroxysteroid dehydrogenase) [45,51,79]. It has a slow onset of action (within weeks) and it is considered as first line treatment for adrenocortical carcinoma (ACC) because of its adrenolytic action [80]. Mitotane initial dose isusually 250-500mg daily, slowly escalated to 0, 5-1g/day; it is important to monitor drug levels regularly [51,80]. In patients with ACC a more rigorous and intensified scheme is followed, aiming to obtain therapeutic levels as quickly as possible. Mitotane has also been used as long-term treatment in patients with CD after unsuccessful trans-sphenoidal surgery (TSS) or while awaiting the effects of radiotherapy or when surgery is not possible [81]. In a recent retrospective study of patients with CD treated with mitotane, remission was achieved in 72% of the 67 long-term treated patients, after a median time of 6.7 months with a mean dose 2.6 ± 1.1g/day; 71% of patients with durable remission subsequently experienced a recurrence, after a median period of 13.2 months. Intolerance leading to treatment discontinuation occurred in 29% patients, whereas a pituitary adenoma became identifiable during mitotane treatment in 25% of the 48 patients with initial negative pituitary imaging allowing subsequent TSS [81]. The dose and mitotane plasma levels required to control hypercortisolism in CD were lower than those needed to achieve ACC antineoplastic activity, with medians around 2.7g of mitotane obtaining plasma mitotane levels of 8.5mg/L, respectively; at these doses concomitant mineralocorticoid replacement may not be required [81,82]. Disadvantages of its use include long half-life (up to 160 days), significant gastrointestinal and neurological AEs, hypercholesterolaemia, and less commonly gynecomastia [51]. Mitotane strongly activates CYP3A4 expression, reducing cortisol bioavailability by accelerating metabolism of exogenous steroids, especially hydrocortisone; hydrocortisone replacement dose should be increased while dexamethasone, a strong CYP3A4 inducer, should be avoided. Specific consideration should be paid to the development of hypoadrenalism that can be often mistaken as gastrointestinal AEs. Drug interactions are numerous [2,45,51,83-85]. Mitotane may lead to restoration of gonadal function and fertility; therefore, effective contraception is advisable for female patients [86]. Mitotane induces a large rise in cortisol binding globulin (CBG) such that measurement of total cortisol is unreliable, and it is necessary to rely on plasma ACTH measurement, urinary, serum or salivary free cortisol to avoid an adrenocortical crisis [87].

Combined treatment

Combined treatment remains an attractive option in the medical management of CD as it can achieve rapid control of hypercortisolemia along with minimization of AEs. Normalization of UFC was observed in 45% of 62 patients with CS (84% of those had CD) treated pre-operatively with the combination of ketoconazole (200-600mg/day) and metyrapone (750-1000mg/day) with a median duration of treatment 4 months [88]. The efficacy of concomitantly introduced mitotane, metyrapone, and ketoconazole was proven to be an effective alternative to avoid adrenalectomy to control severe ACTH-dependent CS [89]. However, a high rate of AEs with acute hypoadrenlism was reported in 36% of patients, and liver enzyme elevation was found in up to 82%. The combination of ketoconazole with cabergoline was studied in 14 CD patients resulting in UFC normalization in 79% of them; in contrast, neither drug succeeded to control hypercortisolemia when taken alone as opposed to their combination [90]. In one prospective series of 12 patients with residual hypercortisolemia after TSS for CD, cabergoline and ketoconazole were effective normalizing cortisol levels in 50% of patients; the addition of ketoconazole to cabergoline increased the rates of UFC normalization from the initial 25% when cabergoline was used alone (2-3 mg/week), to 75% when 200-400mg/day of ketoconazole were added [91]. Since corticotroph cells co-express both SSTRS and DR2 [4,92,93] studies on pituitary adenomas imply that chimeric molecules containing both SST and dopamine structural elements (BIM-23A779, BIM-23A760, BIM-23A781, BIM065) may control tumour cell growth and decrease ACTH levels [24,94]. Moreover, in a small cohort of 17 patients with CD displaying mild, moderate or severe hypercortisolemia, the combination of pasireotide, cabergoline and ketoconazole controlled hypercortisolemia in 88%; in contrast only 29% of patients treated with pasireotide monotherapy and 47% when the latter was combined with cabergoline had similar effect. Patients with more severe hypercortisolemia at baseline needed combined schemes to normalize UFC excretion [95]. After pasireotide mono or combination therapy, a subset of patients was operated and *in vitro* studies showed that SST2 mRNA expression levels of adenomas from these patients, who were in remission, were significantly higher than those from patients with elevated preoperative UFC excretion. This study confirmed that glucocorticoid-induced SST2 downregulation might be reversed by cortisol-lowering therapy. Hence, a preliminary study described a further decrease in UFC in 4 ketoconazole-treated patients after addition of octreotide [95]. Finally, the effect of osilodrostat combination with pasireotideis under investigation in rats [96,97].

Glucocorticoid antagonist

Mifepristone: It is the first potent glucocorticoid antagonist available for clinical use [45,98]. Mifepristone binds to GR with an 18-fold higher affinity than cortisol, resulting in a loss of negative feedback effects at the hypothalamic-pituitary-axis (HPA) by cortisol, leading to an increase in ACTH secretion with a concomitant increase of cortisol production [99]. Mifepristone should be started at 300mg/day and be titrated slowly, since treatment with 400-800mg/day may rapidly reduce the

symptoms and signs of CS; dose adjustment should be based on clinical parameters, since cortisol levels cannot be used as marker of efficacy and the patient can become addisonian unless care is taken [2]. The SEISMIC (Study of the Efficacy and Safety of Mifepristone in the Treatment of Endogenous Cushing Syndrome) suggested that most clinical responders received doses ≥ 600 mg/day, suggesting that higher doses were required to achieve optimal clinical benefit in patients with endogenous CS [100]. Mifepristone gained the approval to control carbohydrate metabolism abnormalities (CHA) secondary to hypercortisolism in patients with CD who failed surgery or were not considered to be good surgical candidates. In a 24-week prospective multicenter trial, 50 adults (43 with CD) with endogenous CS were treated with doses ranging from 300-1200mg/day and obtained improved BP and/or CHA (38% and 60%, respectively), along with a 87% improvement in other features of CS with hypoadrenlism reported in only 4% of patients [99]. Due to mifepristone's long half-life and high affinity for the GR, supraphysiological doses of dexamethasone (2-8 mg/day) are needed to overcome GR antagonism [24]. Similar results were confirmed in 88% of patients who had failed multimodality therapy in a 24-week study [101]. On the other hand, mean ACTH levels increased by > 2-fold in 27/43 patients with CD followed for a median of 11.3months. Tumour regression was seen in 2 patients whereas tumour progression was observed in 3 patients with macroadenomas; a microadenoma was identified after 25months of treatment in a patient with a baseline tumour-negative MRI [102]. Mifepristone showed improvement of clinical signs in 75% of patients with CS of different aetiologies [103] and a maintenance of weight loss was evident at 2-year follow-up [104]. Dosages > 1000mg/day administered for long periods seem to be associated with more AEs mostly manifested as increased mineralocorticoid action (hypertension, hypokalemia, edema) which needed treatment with spironolactone and potassium replacement [105], hypoadrenlism (fatigue, nausea, vomiting, arthralgias, headache) [45,102,103], and endometrial thickening [2]. Mifepristone should not be administered with drugs that are metabolized by CYP3A (ketoconazole) or CYP2C (simvastatin, cyclosporine, fentanyl, ciprofloxacin, non-steroidal anti-inflammatory drugs, warfarin) because of an increased toxicity risk [45] and drugs that increase QT interval, such as pasireotide [106].

Novel inhibitors of cortisol secretion

In murine pituitary tumour cells, doxazosin, an α1-adrenergic receptor antagonist, reduced phosphorylated retinoblastoma protein levels and induced G0-G1 cell-cycle arrest with decreased tumour growth and reduced plasma ACTH levels [45,107]. Normal pituitary and corticotroph adenomas express epidermal growth factor receptor (EGFR) EGFR, which controls POMC expression.

Gefitinib: After blocking of EGFR with gefitinib, a tyrosine kinase inhibitor (TKI), POMC expression was attenuated, with inhibition of corticotroph cell proliferation inducing apoptosis. Gefitinib dose-dependently inhibited POMC-mRNA expression in primary cultures of human corticotroph adenoma cells, while decreased POMC mRNA expression and inhibited ACTH secretion in 6 out of 10 and in 4 out of 12 cultures of canine corticotroph adenomas, respectively; tumour growth was inhibited by 40%. Serum corticosterone levels were also decreased, associated with improvement of clinical signs (fat accumulation, hyperglycemia, weight gain) [108]. Ubiquitin-specific peptidase 8 (USP8) gene is mutated in 33-66% of patients with CD and these mutations, impair EGFR downregulation, increasing activity, signaling and ACTH secretion and increase SSTR5 expression [109].

Bevacizumab: It is a monoclonal antibody that blocks vascular endothelial growth factor receptor 2 (VEGFR2) which is associated with extrasellar extension and greater pituitary adenoma proliferative potential. Its use was shown to inhibit tumour progression and obtain control of hypercortisolemia in patients with CD [110].

R-roscovitine (seliciclib;CYC202): It is a cyclin-dependent kinase inhibitors (CDKI), specifically a CDK2/cyclin E inhibitor, a tumour suppressor which suppressed ACTH expression/production and inhibited tumour growth in transgenic POMC-pituitary tumour transforming gene (PTTG)-1 zebra fish embryos and in a mouse model of ACTH-secreting pituitary adenomas [111]. Currently, a phase II clinical trial (clinicaltrials.gov; NCT02160730) in patients with CD is ongoing to evaluate the efficacy and safety of R-roscovitine.

Selective, peptide melanocortin-2 receptor antagonist, IRC-274: It was identified as a melanocortin-2 receptor (MC2R) antagonist that inhibits binding of ^{125}I-hACTH 1-24 to the human MC2 receptor in a competitive, dose-related manner. Moreover, it was shown a significant in vivo reduction of circulating corticosterone in two rodent models of CD with IRC-274. These observations could lead to the development of a novel therapeutic agent for the normalization of cortisol levels in CD patients [112].

DISCUSSION AND CONCLUSION

There is no effective medical therapy that directly and reliably targets the ACTH-secreting pituitary adenoma. The mainstream of treatment involves medications targeting the adrenal remains in the pre-operative period or while awaiting for the delayed effects of radiotherapy, or when patients cannot be surgically treated. However, it must be noted that, the efficacy of the commonly used metyrapone and ketoconazole have been studied only retrospectively. On the other hand, new agents have been tried such as pasireotide and cabergoline, targeting the receptors of corticotrophs with promising results. Novel therapies aim at the molecular pathways, tyrosine kinases or components of cell cycle. Combined management involving pituitary adenoma targeting treatment and/or inhibition of cortisol secretion and action, may actually represent the best therapeutic approach for effective control of hypercortisolemia and lower drug dosages with the less AEs, although there is lack of enough evidence, and further studies have to support this notion.

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