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HOW BEST TO MONITOR THE SPECIFIC SIDE EFFECTS OF MEDICAL TREATMENTS OF CUSHING'S DISEASE

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ABSTRACT

The first-line treatment of Cushing's disease is transsphenoidal surgery. Medical treatment of Cushing's disease can be considered in several situations: as a presurgical treatment in patients with severe comorbidities, when surgery fails, or while waiting for the maximal efficacy of radiation techniques. Several modalities of medical treatment are possible, from adrenal-targeting drugs (steroidogenesis inhibitors) to pituitary-targeting drugs (somatostatin receptor ligand pasireotide or the dopamine agonist cabergoline), or even drugs that antagonize the glucocorticoid receptor (mifepristone). Given the morbidities associated with hypercortisolism, and the fact that medical treatment can be delivered on a long-term basis, it is important to obtain eucortisolism and to monitor the drug effectively. The efficacy of these drugs will not be detailed in this review, nor their roles in the therapeutic algorithm of Cushing's disease. This review will rather focus specifically on adverse events associated with these drugs (ketoconazole, levoketoconazole, metyrapone, osilodrostat, pasireotide, cabergoline and mifepristone), and the way in which to monitor and treat them, based on retrospective studies and the most recently published prospective studies.

INTRODUCTION

The first-line treatment of Cushing's disease is transsphenoidal surgery. It usually leads to remission in 30-80% of cases when taking into account the mid to long-term risk of recurrence. The medical treatment of Cushing's disease can be considered in several situations: as a presurgical treatment in patients with severe comorbidities, when surgery fails, or while waiting for the maximal efficacy of radiation techniques to be obtained. Several modalities are possible from drugs that target the adrenals (steroidogenesis inhibitors such as ketoconazole, levoketoconazole, metyrapone or osilodrostat; mitotane will not be discussed in this review as its first-line use is mainly adrenal carcinoma, nor etomidate which is usually delivered in life-threatening hypercortisolism), to drugs that target the pituitary (the somatostatin receptor ligand pasireotide or the dopamine agonist cabergoline), or even a drug aimed at antagonizing the glucocorticoid receptor (mifepristone). The aim of this review is not to detail the efficacy of these drugs, or the reasons why some drugs would be preferred over others in specific situations, as this has been the subject of several reviews and guidelines over the last 5 years (1-4). Here, we will focus only on the tolerance profile of all these drugs when delivered as a treatment for hypercortisolism. It is important to consider that some of these drugs have been used for decades, and reported only in retrospective studies, while others have only been reported in prospective randomized studies, thus leading to a more exhaustive recording of side effects. A strict comparison of the tolerance of all of these drugs is thus not possible. Hence, we will rather detail the side effects, and the way in which to control them, or even, to anticipate them. The tolerance of the association of drugs, which is usually used in severe hypercortisolism, will not be covered in this review.

1. STEROIDOGENESIS INHIBITORS

The use of all of these drugs can theoretically lead to adrenal insufficiency. The prevalence of adrenal insufficiency will be given for each drug, but this specific point will be addressed through the prism of a titration approach. Any patient on steroidogenesis inhibitor should be educated on the clinical signs of adrenal insufficiency, have a prescription of hydrocortisone, and be warned to call the treating endocrine department (or go to the emergency department) in case of suspicion of adrenal crisis. Anorexia, nausea and diarrhea, which can be associated with the use of each drug independently of cortisol levels, should always be considered first as signs of adrenal insufficiency. Of note, the "block and replace" approach, in which a higher dose of drug is provided to reach a state of adrenal insufficiency then replacement is carried out with hydrocortisone, is a way to avoid the risk of adrenal insufficiency.

a. Ketoconazole

Ketoconazole is an imidazole agent that blocks several steps in the steroidogenesis pathway (1). It was first marketed as an antifungal agent but has been used for the treatment of Cushing's syndrome for more than 30 years. This explains why a prospective randomized study has never been performed with this drug. Data on tolerance are thus from large retrospective studies, or from observational prospective studies.

- Liver enzyme increase

Stricker et al. reported on a clinicopathological study of 55 cases of ketoconazole-associated hepatic injury (used for non-hypercortisolic etiologies) in 1986. In 60% of cases, liver toxicity appeared in the first 6 weeks after commencing ketoconazole: the biochemical pattern was hepatocellular in 54% cases, cholestatic in 16%, and mixed in 30%. The authors recommended weekly monitoring of liver enzymes for the first 6 weeks, and then every 2 weeks for 6 months, and then every month thereafter (5). Acute liver injury has been reported only rarely, and this is also the case for fatal ketoconazole-induced hepatitis (1/15,000 cases) (6-8).

In Cushing's syndrome, the first reports of ketoconazole use were reassuring (9, 10). However, more recent studies have suggested that liver tolerance should indeed be one of the main criteria to monitor while on ketoconazole treatment. In the largest retrospective multicenter study reported, based on 200 patients, 41 (25.6%) patients had to stop the drug because of side effects. Among

these, increased liver enzymes were the most frequent side effect: a less than 5-fold increase was reported in 15.8% of patients, while a 5-10-fold increase was reported in 2.1% (n=4 patients). One patient, simultaneously consuming alcohol and taking acetaminophen, presented a 40-fold increase in liver enzymes; increased liver enzymes then returned to normal when ketoconazole was decreased or stopped for 2-4 weeks. Interestingly, no correlation was observed between the dose of ketoconazole and the occurrence of liver enzyme increase, suggesting that this side effect could be observed at the lowest dose (range 200-1200 mg/day), or indeed at any dose change. Liver enzyme increase always occurred during the first month after commencing the drug, or after a change in dose, suggesting the need to have strict monitoring (every 7 days) at least during these periods (11). These data were in agreement with an observational prospective French cohort study (compassionate use program) which was reported a few years later, and specifically focused on liver tolerance in 108 patients treated with ketoconazole for Cushing's syndrome. When only considering patients who were naïve to ketoconazole treatment (n=47), 4 patients (8.5%) presented with moderate asymptomatic liver enzyme increase, considered to be ketoconazole-related in 3 cases (and this was observed during the first month of treatment) (12).

Interestingly, in the case of skin diseases, a spontaneous decrease in liver enzymes has been reported in patients with abnormal liver enzymes at the time of commencing ketoconazole, with a disappearance of hepatotoxic mycotoxins, thanks to ketoconazole treatment. A somewhat similar effect has been reported in patients treated with hypercortisolism, which can lead *per se* to liver enzyme increase; ketoconazole-induced eucortisolism may thus improve liver enzymes in such patients, which means that a moderate liver enzyme increase (less than 2-3-fold above normal values) should not be considered a formal contra-indication for ketoconazole use, provided strict monitoring is performed (13).

- Adrenal insufficiency and other side effects of interest

In their recent meta-analysis on steroidogenesis inhibitors, Melinda et al. reported the occurrence of diarrhea and abdominal pain in 8% of cases, rash in 3% and adrenal insufficiency in 6% of cases (the analysis was based on 366 patients reported in the literature). This is in agreement with the largest French retrospective study, which reported 5.4% of patients with adrenal insufficiency in 200 patients treated with ketoconazole. While adrenal insufficiency was expected in 3 patients treated with a block and replace approach, it occurred in 7 patients during the titration phase (mean dose of 700 mg/day).

Hypogonadism and gynecomastia may occur in men as a consequence of decreased testosterone secretion by the testes (14, 15). This is one reason which explains why some investigators prefer to use ketoconazole in females than males. Finally, ketoconazole increases the QT interval, leading to an increased risk of torsades de pointe. Due to the high number of interacting drugs, this should be carefully monitored while on treatment. Of note, De Martin et al. reported the lack of long-term appearance of increased QTc in 15 patients treated with ketoconazole for a median duration of 7 months, and this side effect should be particularly monitored at the onset of ketoconazole (16).

- How to anticipate side effects?

Ketoconazole treatment should not be initiated in patients with liver enzymes that are > 3-fold normal values. The liver toxicity does not seem to be correlated with dose, and this can occur any time during follow-up. However, the periods at risk are probably the first 60 days, and for at least 1 month after each change in dose. Liver enzyme monitoring should be performed on a weekly basis during at least 1 month after commencing treatment or after dose change. Patients should be warned of signs of liver toxicity such as jaundice, even if, in most cases, liver enzyme increase remains asymptomatic. In case of liver enzyme increase, the ketoconazole dose should be decreased, or treatment should be withdrawn, with liver enzyme follow-up maintained until they return to normal. An EKG should be done before treatment commences and also at each dose change.

b. Levoketoconazole

Levoketoconazole is a 2S, 4R enantiomer of ketoconazole. Preclinical findings have suggested that levoketoconazole might be a more potent inhibitor of cortisol synthesis than ketoconazole, and with

a lower risk of liver toxicity. However, a clear-cut comparison is difficult as the design of studies for levoketoconazole and ketoconazole have not been the same (for levoketoconazole, a phase 3 open label single arm study (SONICS), a double-blind placebo-controlled withdrawal study (LOGICS) and an ongoing open label long-term safety study (OPTICS), while mainly retrospective studies have been published for ketoconazole) (17).

- Increase in liver enzymes

In the SONICS study, a moderate ALT increase was reported in 15% of cases, while major ALT increase was seen in 1 patient. Looking in greater detail, a > 3-fold ALT increase was observed in 11% of cases, including a > 5-fold in 3%. The risk period for liver toxicity appeared similar with a maximal risk observed 2 months after the starting of levoketoconazole (18). In the maintenance phase of SONICS, based on 94 patients, 10 patients presented at least one ALT elevation of more than 3x ULN, including 3 with greater than 5x ULN (18). In the LOGICS study, 79 patients received levoketoconazole in a phase 3, placebo-controlled, randomized-withdrawal study with open-label titration-maintenance (14–19 weeks) followed by double-blind, randomized-withdrawal (8 weeks), and restoration (8 weeks) phases. The mean duration of levoketoconazole exposure was 160 days with a mean daily dose of 538 mg. ALT values above the normal range occurred at least once in 45% of the patients: however, levels that were > 3x ULN were observed in 6 patients (7.2%), and > 5x ULN in 3 patients (3.6%). When abnormal liver enzyme evaluation was seen, a return to normal values was obtained after a mean of 4 weeks of drug withdrawal. Again, the median first time to ALT increase was roughly 60 days (19).

- Adrenal insufficiency and other side effects of interest

Adrenal insufficiency was reported in 9.5% of the patients in the different phases of the LOGICS study, and especially in 4.5% during the randomized phase of the study. No patient had a block and replace regimen. While a tendency for increased testosterone levels were observed in males in the SONICS study, this trend was not confirmed in the LOGICS study, as both males and females presented decreased testosterone levels while on levoketoconazole. Finally, while in the SONICS study, QT interval prolongation was reported in 5.3% of cases, it was observed at least once in 20.2% of the 84 patients analyzed in the LOGICS study. When QT interval prolongation was defined as superior to 500 milliseconds, only 3.6% of the patients presented this side effect.

- How to anticipate side effects?

Roughly 5-15% of patients will present increased liver enzyme while on levoketoconazole. We thus think that the drug should not be initiated in patients with liver enzyme increase > 3-fold-normal values, and weekly monitoring of liver enzymes should be carried out during the first 2 months of treatment, and probably at each dose change. Patients should be warned of signs of liver toxicity such as jaundice, even if, most of the time, the increase in liver enzymes remains asymptomatic. In case of liver enzyme increase, the dose of levoketoconazole should be decreased, or treatment should be withdrawn, with liver enzyme follow-up maintained until they return to normal. An EKG should be performed before starting drug treatment and again at each dose change.

c. Metyrapone

Eleven-beta hydroxylase is the main steroidogenesis enzyme target of metyrapone. This leads to a decrease in cortisol, but also to increased levels of precursors (11 deoxycortisol and 11-deoxycorticosterone), leading to a theoretical phenotype of hyperaldosteronism with frequent hypokalemia and hypertension, even though metyrapone is also a blocker of aldosterone synthase (1). The results of a recent prospective study (PROMPT study) have only been reported as an abstract up to now and will not be included in this chapter.

- Hypertension, hypokalemia and hyperandrogenism

The first retrospective study, on 13 patients treated for a mean of 21 months, was reported in 1977 (20). None of the patients presented worsening of hypertension or hypokalemia, nor water retention causing leg edema. Of the seven women treated, five declared a worsening of hirsutism and/or acne, including one who considered it too severe to continue using the drug. In 1991, Verlhé et al. reported the retrospective results of metyrapone in 91 patients with Cushing's syndrome, including

57 with Cushing's disease: analysis of side effects was possible for 75 patients. The authors did not mention any worsening of hypertension (81% patients had hypertension before commencing, and hypertension improved in 73%), while they described leg edema in 6 patients, which improved with a short course of diuretics. They also described mild transient hypokalemia (2.9-3.3 mEq/L) in 5 patients who had normal potassium levels at diagnosis. The patients responded well to potassium supplements. Finally, hirsutism and/or acne was seen in 9/16 women (56.2%) treated with metyrapone: no mention of worsening was reported by the authors who reported that 6/9 already (66.6%) had hyperandrogenism at diagnosis (21). In the largest retrospective multicenter study reported to date, based on 195 patients, side effects were noted in 48/195 patients (24.6%) treated with metyrapone, with only 12% requiring admission because of their grade. The mean dose at the time of onset of side effects was 1600 mg/day. Interestingly, most side effects occurred during the 15 days following starting treatment or dose change. Hypokalemia was not reported: however, the authors stated that "potassium levels were monitored and actively treated at presentation and during therapy": mean potassium levels increased from 3.68 to 3.9 mmol/L while on metyrapone. Hypertension was present in 64.6% of patients at diagnosis, and the authors did not mention any worsening while on treatment. Surprisingly, there was no mention of hyperandrogenism in the retrospective data obtained, except for 1 patient with a worsening of acne (22). Finally, Ceccato et al. reported the use of metyrapone (median dose of 1000 mg/day, for a median period of 9 months) in a recent observational study on 31 patients (including 20 with Cushing's disease). Twenty four out of thirty one (77.4%) patients were hypertensive at diagnosis: during metyrapone treatment, 2 normotensive patients presented with hypertension controlled with medical monotherapy, while 5 hypertensive patients needed an uptitration of their treatments. None of the 31 patients presented with worsening of hypokalemia. Ten of nineteen females (52.6%) presented increased androgens, including 5 who complained of hirsutism (and 1 of alopecia). Interestingly, 7 of these 10 patients also presented with hypertension worsening at the same time. Spironolactone (100-200 mg/day) treatment resulted in decreased symptoms, and symptoms finally resolved with decreased doses of metyrapone (23).

- Adrenal insufficiency and other side effects of interest

Verhelst et al. reported that 10/79 patients (12.7%) presented adrenal insufficiency while on metyrapone: 4 of these patients presented this during an infection, while the remaining patients had adrenal insufficiency due to overtreatment. Symptoms resolved with temporary glucocorticoid supplementation, and a decreased dose of metyrapone (21). Similar results were reported by Daniel et al. in 195 patients, of whom 7% presented with hypoadrenalism, treated with switch to a block and replace approach (unchanged metyrapone and glucocorticoid supplement) or a decreased dose of metyrapone and temporary use of glucocorticoid supplements. Finally, in a recent meta-analysis, based on 89 patients treated with metyrapone for Cushing's disease, nausea was reported in 18% of patients, vertigo in 17% and fatigue in 7% (24). Daniel et al. reported that gastro-intestinal side effects were the main reasons for drug withdrawal in their retrospective study on 195 patients (24).

- How to anticipate the side effects?

Hypertension and hypokalemia should be closely monitored during the first 15 days after commencing treatment, and at each dose change. Patients with severe hypertension and hypokalemia might benefit from potassium supplementation and spironolactone before starting metyrapone; in that specific case, combined treatment with metyrapone and ketoconazole might neutralize the side effects of metyrapone in terms of hypertension and hypokalemia by blockade of different steroidogenesis pathways. Hyperandrogenism seems to be a frequent dose-dependent side effect which could be improved by spironolactone. This is one of the reasons why some investigators prefer metyrapone rather than ketoconazole as a first line treatment in men with hypercortisolism.

d. Osilodrostat

Osilodrostat is another 11-beta hydroxylase inhibitor, with an overall mode of action comparable to metyrapone, though seemingly more effective in vitro for blocking cortisol secretion (25). It was initially designed as an antihypertensive agent thanks to its blockade of aldosterone synthase. It also

leads to increased levels of precursors (11 deoxycortisol and deoxycorticosterone), with a theoretical risk of hypertension and hypokalemia (26). Osilodrostat has the advantage of several prospective clinical trials published over recent years (while retrospective data on a large French cohort should be published soon).

- Hypertension, hypokalemia and hyperandrogenism

Tolerance data were mainly extracted from 2 prospective studies. LINC-3 was a 48-week prospective study with an 8-week double blind placebo-controlled phase (137 patients included), which was then prolonged with a study extension (more than 48 weeks of treatment and a mean osilodrostat exposure of 130 weeks): 12/106 patients (11.3%) discontinued the treatment during the extension phase, vs. 15/137 (10.9%) during the core phase, because of side effects(27, 28). In LINC-3, 19 patients presented with hypertension and 17 with hypokalemia during the core study vs. 13 and 5 during the extension phase, respectively. Increased blood testosterone was reported in 17 patients during the core study vs. only 1 additional patient during the extension study. LINC-4 was a phase III, multicenter trial with an initial 12-week randomized, double blind, placebo-controlled period, followed by a 36-week, open-label treatment period. Among the 73 patients included, hypertension was reported in 21.9% of the patients by the end of the study. The most common grade 3/4 side effect (reported in 38.4% of the whole cohort) was hypertension, reported in 13.4% of the patients. Interestingly, potassium levels remained stable and within the normal range during treatment, but antihypertensive treatments leading to increased potassium could be provided at any time during the study. Finally, among female participants, testosterone became greater than ULN in 40.9% of patients by week 12, with a further decrease, and 36.1% of patients at data cutoff. This was reported as an adverse event in 29.6% of cases, while symptomatic hirsutism was reported in 9.6% of the patients (29).

Recently, a study compared the profiles of steroidogenic enzyme inhibition by metyrapone and osilodrostat using mass spectrometry (30). In this study, the median dose of osilodrostat was 10 mg/day, while the dose was 1250 mg for patients treated with metyrapone, with a median range of treatment of 7 months. Based on 23 patients controlled by osilodrostat, 13 by metyrapone, and 6 with a switch from metyrapone to osilodrostat, the authors showed that the levels of 11 deoxycortisol were significantly lower in the osilodrostat vs. metyrapone groups. The same was observed for androstenedione and testosterone, concordant with the rate of clinical signs of hyperandrogenism reported by the patients (21 vs 12% in metyrapone vs osilodrostat groups, respectively).

- Adrenal insufficiency and other side effects

In the LINC-3 study, hypocortisolism-related clinical signs were reported in up to 51.1% of cases, but the definition of adrenal insufficiency was sometimes uncertain and could be confounded with glucocorticoid withdrawal syndrome. Indeed, the diagnosis was an investigator-reported adverse event term based on their clinical judgement, while no cortisol measurement was required. Using the same diagnostic criteria, the rate was lower in LINC-4, in which 14.6% patients presented with adrenal insufficiency during the titration phase, for a total of 27.4% at the end of the study. Interestingly, in both the LINC-3 and LINC-4 studies, the rate of adrenal crisis was 1-2%. Most cases of adrenal insufficiency occurred during the titration phase (60% and 58% cases before week 12 in LINC-3 and LINC-4, respectively). The remaining cases occurred after week 12, sometimes after prolonged use of osilodrostat (27-29). We recently reported a risk of delayed adrenal insufficiency in 1 patient treated with osilodrostat on a stable dose for more than 12 months (31). In the spectrometry study discussed above, the risk of adrenal insufficiency was higher in the osilodrostat vs. metyrapone group, being 16 vs 0% by clinical data, and 48 vs 7% by spectrometry data, respectively (30).

Finally, the most frequent side effects were arthralgia, decreased appetite, fatigue and nausea in the LINC-3 and LINC-4 studies. Less than 10% of these cases were considered grade 3 or 4. In LINC-4, 3 patients (4.1%) presented with an increased QTc (29).

- How to anticipate the side effects?

Hypokalemia and hypertension should be closely monitored after starting treatment, and at each dose change. Spironolactone might be considered as systematic treatment, especially in patients

with hypertension. Potassium supplementation is another possibility. Patients treated with osilodrostat should receive detailed education on adrenal insufficiency, and a supply of hydrocortisone tablets. There is no clear consensus on whether osilodrostat should be used in a block and replace approach (high dose of osilodrostat, and systematic glucocorticoid supplementation) or via a titration approach. In the case of suspicion of adrenal insufficiency, the drug should be temporarily withdrawn or the dose decreased, or glucocorticoid supplementation could be added, as shown in the LINC-4 study: based on the investigator's decision, because of the clinical and/or biochemical suspicion of adrenal insufficiency, osilodrostat was temporarily withdrawn in 15 patients, the dose decreased in 6 patients, and 13 patients received concomitant hydrocortisone (29).

2. PITUITARY-TARGETED DRUGS

a. Pasireotide

Pasireotide is a somatostatin receptor ligand (SRL) with high affinity to all somatostatin receptor subtypes, with the exception of subtype 4. It is thus of theoretical interest in Cushing's disease due to its high affinity for somatostatin receptor subtype 5, the most abundantly expressed somatostatin receptor in corticotroph tumors. An extensive safety profile of pasireotide in pituitary diseases has been recently published (32). We will thus only describe here some points of interest, focusing on the safety profile of long-acting release pasireotide.

The main difference in side effects, when compared with first generation somatostatin receptor ligands, is the risk of hyperglycemia/diabetes. Diabetes was reported in 13.6-46.2% of cases with pasireotide LAR, while glucose disturbance was reported in an additional 22.7 to 46.2% of the patients treated for acromegaly or Cushing's disease. The phase 3 trial on LAR pasireotide in Cushing's disease included 150 patients randomly assigned to 10mg (n=74, median treatment duration 449 days) or 30 mg (n=76, median treatment duration 381 days) of pasireotide. All patients except one presented at least one adverse event, the majority being of mild to moderate severity. Hyperglycemia-related adverse events occurred in 72% and 83% of patients treated with 10 and 30 mg respectively, and this was considered a serious adverse event in 23 and 24% of these patients, respectively. As a result, 4 patients per group discontinued pasireotide. Of the patients with normal glucose levels at baseline, 37% (13/35) and 23% (7/31) developed prediabetes while on pasireotide at 10 and 30 mg, respectively, while 54 and 68% became diabetic at least once during the study (33). In the phase 3 extension study (34), 81/150 patients entered the study, for a median period of 23.9 months (48.1% of the patients were treated for at least 12 months): 91.4% experienced at least one adverse event during the extension study, including 38.3% with grade 3 or 4 adverse events. Looking in greater detail, 39.5% (n=32) experienced at least one hyperglycemic adverse event, leading to drug withdrawal in 3 patients.

The main mechanism of pasireotide-induced hyperglycemia is linked with reduced insulin secretion due to somatostatin receptor subtype 5 binding in pancreatic islet cells. Guidelines have been published on the optimal way to treat these patients: first line treatment should be by metformin, DPP-IV inhibitor or GLP-1 receptor agonist; insulin should be used only in patients with a major increase in blood glucose (35). Recently, a multicenter randomized open label phase IV study focusing on subcutaneous pasireotide-associated hyperglycemia included 59 patients with Cushing's disease was published. Twenty five patients were randomized to insulin vs. incretin; the remaining 34 were followed (6 had insulin at baseline, 13 had an antidiabetic drug, and 15 had no treatment). The results showed no significant difference in terms of improvement of HbA1c between insulin and incretin; based on the observational phase of the study, the authors concluded that metformin should be considered a valid first line treatment; based on the randomized section of the study, they concluded that incretin should be associated as a second line treatment (36). These results suggest that pasireotide should not be used in patients with Cushing's disease and unstable diabetes; and that blood glucose and HbA1c should be closely monitored in all patients while on pasireotide treatment.

Other side effects appear to be similar to those reported with first generation SRLs, including diarrhea (16-38.6%), cholelithiasis (24-45% in the phase 3 trial with 10 and 30 mg pasireotide, including 4 patients who required cholecystectomy), headache (3-28.6%), abdominal pain (8-18.2%) and alopecia (2-18%) (32). These side effects appear to become less frequent when the treatment is prolonged, as suggested by the phase 3 extension study results (34).

b. Cabergoline

Due to the expression of dopamine D2 receptors on corticotroph adenoma cells, cabergoline has been considered a potential treatment of Cushing's disease. Published data are scarce, mainly based on small series (126 patients reported in a total of 7 studies, the majority with a follow-up inferior to 6 months), except for the French retrospective study published in 2017 (37). In this study, 66 patients received cabergoline as monotherapy or combination. Interestingly, 5 patients developed corticotrophic insufficiency while on cabergoline monotherapy. Safety data were available for 57 patients, with a mean duration of 28 months of cabergoline (in 21 responders, mean dose 1.5 mg/week), and 4 months (in non-responders, mean dose 3.5 mg/week). Classical short-term side effects were similar as those reported for cabergoline in prolactinoma (dizziness, nausea, asthenia or hypotension were reported in roughly a third of the patients). The drug was withdrawn in 8 patients (13%) because of poor tolerance, including one with a grade 2 aortic insufficiency (though the patient had no ultrasound prior to treatment and the short duration of cabergoline makes it unlikely for it to be related to this valvular disease). One patient with a history of depression presented a manic episode, and improved after cabergoline withdrawal. The relatively small cohort and short follow-up do not allow firm conclusions to be drawn on the long-term side effects of this drug, but there is no reason to suspect that they would be different from those reported for cabergoline treatment in prolactinoma (38). This means that cardiac ultrasound should be performed before starting the drug, and at regular intervals in those patients treated with high doses of cabergoline on a long term basis.

3. THE GLUCOCORTICOID RECEPTOR ANTAGONIST MIFEPRISTONE

Mifepristone is the only available glucocorticoid receptor antagonist, and has an affinity for the glucocorticoid receptor which is 10-fold higher than that of cortisol (39). The mechanism of action leads to side effects mainly via 2 mechanisms: first, the blockade of pituitary glucocorticoid receptors leads to increased ACTH levels, and hence, increased cortisol levels, which can activate the mineralocorticoid receptor; second, mifepristone also has an antiprogestin activity, leading to a relative hyperestrogenism. In 2012, we summarized the retrospective data from the literature on mifepristone use in Cushing's syndrome, based on retrospective series of cases, and this showed hypokalemia in roughly 33% of the 37 published patients, and adrenal insufficiency in 16% (40). Since then, a prospective study, and a few retrospective series have clarified the safety profile of the drug. As with any drug aimed at controlling hypercortisolism, mifepristone treatment has a risk of adrenal insufficiency. Here, adrenal insufficiency is not due to low cortisol levels, but to the inability of cortisol to bind to glucocorticoid receptors. For patients treated with mifepristone, the diagnosis and management of adrenal insufficiency raises 2 major issues: firstly, the diagnosis is difficult because it cannot be based on cortisol levels, which are increased. Clinical symptoms are also difficult to analyze, as the published data suggests that mifepristone can lead to nausea and vomiting. Secondly, the classical management of adrenal insufficiency is not effective: hydrocortisone is not able to bind to glucocorticoid receptors while on mifepristone, and the management of adrenal insufficiency thus requires high doses of dexamethasone for a prolonged period (2-8 mg daily for 1-12 days in (41)). In the only prospective study reported to date (SEISMIC trial, Study of the Efficacy and Safety of mifepristone in the treatment of endogenous Cushing syndrome, phase 3, 24-week, open label multicenter study) 24/50 patients (48%) presented with nausea; adrenal insufficiency was reported in 2 patients, but 5 additional patients presented with symptoms suggesting adrenal insufficiency. In the same study, 22 patients (44%) had potassium levels below 3.5 mEq/L, including 3 patients with potassium below 2.5 mEq/L; twelve patients (24%) presented with hypertension while on mifepristone, and it was associated with signs of mineralocorticoid receptor activation in 9 of these

patients (75%). Management included potassium supplementation in all patients, and spironolactone in 14 patients (41). In a post-hoc analysis of the SEISMIC study, the authors reported that the non-specific side effects (headache, arthralgia, dizziness and decreased appetite, seen in 20-40% of cases) were not associated with the dose, and occurred more frequently at the beginning of the titration phase, while the risks of hypokalemia and hypertension remained stable over time (42). As a comparison, in a series of 16 patients treated with mifepristone for ectopic ACTH secretion, only 1 patient (6.3%) presented hypokalemia, while increased blood pressure was reported in 31% of cases (43).

Mifepristone can also lead to endometrial thickening with vaginal bleeding because of the blockade of progesterone receptors: endometrial thickening was reported as a side effect in 10 patients, and vaginal bleeding in 5 premenopausal women in the SEISMIC study, at the end of 24 weeks of mifepristone treatment (41).

CONCLUSIONS

Cushing's disease is generally difficult to manage since transsphenoidal surgery does not cure all patients, and medical treatment is frequently required on a long-term basis. This implies the need for obtaining eucortisolism, which is sometimes difficult to determine with the currently available biochemical tools (assays of urinary free cortisol, salivary cortisol...) (26). It is thus important to know the safety profile of each of these drugs and the period after commencing treatment at which patients are the most at-risk of side effects. Most of these drugs will present side effects on commencing treatment and at each dose change, for the following 2-8 weeks. In most cases, such side effects will not continue on a long-term basis. Rare cases of delayed side effects mean that the monitoring should however be maintained. More importantly, for adrenal insufficiency, patients should be educated concerning the symptoms which are suggestive of a side effect (nausea, vomiting, diarrhea, unusual and intense fatigue, even if this can be confounded with glucocorticoid withdrawal syndrome). Of note, each of these side effects is usually quite easy to manage, provided optimal monitoring is carried out (see Table 1). The large number of drugs now available for treating hypercortisolism, and the possibility to associate these to decrease the dose and improve the safety profile, should allow for an individualized management for each patient in the future.

Table 1

Drug	Main side effects	Suggested monitoring
Ketoconazole	-Liver enzyme increase -Hypogonadism	-Liver enzymes measured every week for 1-2 months at start of treatment, and then at each dose change for an additional month. Maintenance of liver enzyme monitoring on a long-term regular basis -Clinical evaluation
Levoketoconazole	-Liver enzyme increase -Hypogonadism	-Liver enzymes every week for 1-2 months at start of treatment, and then at each dose change for an additional month. Maintained liver enzyme monitoring on a long-term regular basis -Clinical evaluation
Metypapone	-Hypokalemia and hypertension -Hyperandrogenism	-Clinical and biological monitoring during the first 15 days following the start of treatment, and then at each dose change for 15 days. -Clinical evaluation
Osilodrostat	-Hypokalemia and hypertension -Hyperandrogenism	-Clinical and biochemical monitoring during the first 15 days following start of treatment, and then at each dose change for 15 days. -Clinical evaluation
Pasireotide	-Hyperglycemia and diabetes -Gastro-intestinal symptoms, Cholelithiasis	-Regular monitoring of blood glucose and HbA1c during the whole period of treatment (but generally happening at the start or at each dose change) -Clinical evaluation, regular liver ultrasound
Cabergoline	-Hypotension, dizziness, nausea -Heart valvular disease	-Clinical evaluation -Clinical evaluation and heart ultrasound depending on the dose and the period of exposure (similar to prolactinoma)
Mifepristone	-Hypertension and hypokalemia -Endometrial thickening	-Regular monitoring of blood glucose and HbA1c during the whole period of treatment (but generally happening at the start or at each dose change) -Yearly endometrial ultrasound

Suggested monitoring for the main specific side effects of drugs used in Cushing's disease. Adrenal insufficiency can be seen with all of these drugs. Patients should be educated on the symptoms and be provided with a prescription of hydrocortisone to be used. Cortisol measurement cannot be used for patients on mifepristone.

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