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Cushing's disease: role of preoperative and primary medical therapy

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Abstract

Transsphenoidal surgery is the first-line treatment for Cushing's disease. However, some situations may require the use of a primary medical treatment, such as in patients with severe life-threatening hypercortisolism, a situation which can be handled by fast-acting steroidogenesis inhibitors, instead of classical bilateral adrenalectomy. Primary medical treatment could also be considered in patients with non-severe hypercortisolism, but the evidence is far less convincing for its systematic use. The aim of this short review is to explain briefly the different circumstances in which primary medical therapy could be considered, the limits of this approach, and the way in which to initiate and monitor the treatment.

Introduction

Primary medical therapy (PMT) can be considered in Cushing's disease in patients for whom transsphenoidal surgery is contra-indicated or is refused by the patient (1). Except for patients in very poor health, a permanent surgical contra-indication is rare, given improvements in surgical techniques and the low morbidity of the transsphenoidal approach. PMT thus mainly applies to patients with severe comorbidities due to hypercortisolism, i.e. cardiovascular, metabolic, psychiatric, infectious or thrombo-embolic comorbidities (2), all of which require a dedicated symptomatic and preventive treatments (insulin, potassium, anticoagulants, etc.), but also a rapid and often prolonged control of cortisol secretion. However, the lack of prospective studies on PMT explains why the recent Pituitary Society guidelines on Cushing's disease did not recommend systematically using preoperative medical treatment in patients with Cushing's disease (1).

The roles of preoperative and primary medical therapy

Management of patients with severe hypercortisolism has changed drastically over the last 10 years, with studies reporting the benefits of fast-acting steroidogenesis inhibitors either as a single treatment, or more frequently in combination, in patients with severe hypercortisolism due to Cushing's syndrome (3, 4), thus challenging the benefits of classical salvage bilateral adrenalectomy. For example, Kamenicky et al. reported the benefit of a combination of ketoconazole and metyrapone, associated with mitotane (the last being given as a long-term treatment), in 11 patients: median urinary free cortisol (UFC) decreased from 42-times the upper limit of normal to almost normal within 2-7 days, and this was rapidly associated with a major improvement in comorbidities. Other drugs also showed benefits for controlling severe hypercortisolism, including etomidate, mifepristone (5) and more recently osilodrostat, especially in ectopic ACTH secretion (6). In this setting, the main role of PMT is thus to decrease the risk of life-threatening complications (such as pulmonary embolism, hypertensive crisis, myocardial infarction, stroke) to decrease mortality in fragile patients.

However, as severe hypercortisolism is very rarely seen in pituitary-dependent hypercortisolism, the place of PMT in Cushing's disease is much more debatable. Examination of the current PMT approach, using the European Registry on Cushing's Syndrome (ERCUSYN) database, showed that approximately a quarter of the 787 patients with Cushing's disease received a PMT. In these situations of non-severe hypercortisolism, steroidogenesis inhibitors were frequently given as a single treatment, mainly using ketoconazole or metyrapone. Interestingly, the median duration of pretreatment was 107 days, a period which is probably insufficient to allow cessation of treatment for comorbidities (at least 6 months) (7), but sufficient to help control them. This is an issue on which we have reported in a retrospective study of ketoconazole, where 33-50% improvements in diabetes, hypertension, and hypokalemia were seen after 4 months of PMT (8). However, in a patient with well-controlled comorbidities, and if surgery can be performed without delay, the real benefit of lowering cortisol levels to improve comorbidities is controversial: this is particularly true as PMT will decrease cortisol, and hence the negative feedback loop on non-adenomatous corticotrophs, and therefore bias the predictive value of cortisol levels as a factor predictive of remission in the early post-operative evaluation. In the ERCUSYN study, immediate post-operative low cortisol levels were indeed more frequently reported in patients treated by surgery without PMT compared to surgery with PMT. However, only long-term follow-up data will determine whether recurrence will be higher in the latter group, or if PMT biases cortisol evaluation after surgery (9).

Practical use of primary medical therapy

The means of titrating the PMT should also be considered. For example, ketoconazole is usually started at 400 mg/day in non-severe forms, and 800 mg/day in severe forms. For metyrapone, depending on severity, starting doses range from 750 mg to 2250 mg per day (3). However, there is no absolute rule on the starting dose of these 2 treatments. High doses of steroidogenesis inhibitors also create a risk of adrenal insufficiency, and is the reason why some clinicians consider using a "block and replace" approach, giving very high doses of steroidogenesis

inhibitors concomitantly with substitutive treatment with glucocorticoids. "Block and replace" should also be the preferred approach in patients who had a history of adrenal crises while on PMT, or in patients with cyclic Cushing's disease. For osilodrostat, the theoretical starting dose is 2 mg twice daily. In severe forms, given the sometimes delayed optimal efficacy, a higher dose may be initiated immediately, under strict supervision or as part of a "block and replace" approach. In this situation, being certain that cortisol-lowering drugs indeed decrease cortisol to low values can be problematic because it is hydrocortisone that is measured in immunoassays. However, it is imperative to avoid the risk of mild hypercortisolism in these patients who require very rapid control of their disease (10).

In non-severe hypercortisolism, a careful titration of the drug should be performed with combined monitoring of 08:00 am serum cortisol, and several measurements of late-night salivary cortisol and 24-hour urinary free cortisol (11). Importantly, the pharmacodynamic properties of osilodrostat should be kept in mind, as the maximal efficacy of the drug might be delayed and could lead to a premature up-titration and adrenal insufficiency (12). In patients with non-severe hypercortisolism, pituitary-targeted drugs such as pasireotide or cabergoline could be considered: while their anti-secretory efficacy may be lower, they have the advantage of targeting the tumor, which might be of interest in invasive macroadenomas without surgical indication, though it is noted that macroadenomas represent less than 20% of cases of Cushing's disease (1).

The decrease in cortisol levels may also have an impact on the complications, particularly metabolic, of hypercortisolism. Continuous monitoring of blood pressure, blood glucose, and blood potassium levels should be performed throughout the course of the PMT. This will involve regular readjustment of the dose of antihypertensive and antidiabetic treatments and potassium supplementation that may have been initiated at diagnosis. Finally, the decrease in cortisol levels may be the cause of intense fatigue, which may lead to the erroneous diagnosis of adrenal insufficiency, and to a decrease in the dose of PMT. Clinical and biological markers (blood pressure, kalemia) as well as the evaluation of cortisol levels will help to differentiate these 2 situations.

Finally, uncertainty remains regarding the optimal care strategy for patients with Cushing's disease and a negative pituitary MRI. Recent work by Cristante et al. suggests that these patients should undergo surgery, provided it is conducted by an expert neurosurgeon. Indeed, there was no significant difference in remission rates according to the results of preoperative MRI. Interestingly, the authors showed that "negative" pituitary MRI has been replaced by "doubtful" - in the last 10 years (13). It is expected that future imaging will increase the likelihood of identifying the tumor before surgery, thus removing doubt as to the optimal strategy for these patients. Some expert teams still prefer to treat first with a steroidogenesis inhibitor, and regularly monitor the MRI: monitoring data suggested that a pituitary tumor image would become visible after 2-5 years in about a third of cases. Such a monitoring strategy obviously requires strict eucortisolism while on prolonged medical treatment (8).

Conclusion

PMT should be reserved for patients with life-threatening comorbidities of hypercortisolism (with a rapid titration or "block and replace" approach), or contra-indication or refusal of surgery. The place of PMT in patients with non-severe hypercortisolism continues to be debated. In this setting, monitoring should be strict to avoid mild hypo- or hypercortisolism, and a minimum period of 3-6 months of PMT should be considered to improve the comorbidities.

Legend to figure 1: Proposed algorithm for different situations of possible use of primary medical treatment in Cushing's disease. *Some teams might consider primary medical therapy in patients with non-severe hypercortisolism and negative MRI.

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