

# Synergistic cortisol suppression by ketoconazole–osilodrostat combination therapy

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## Summary

Here, we describe a case of a patient presenting with adrenocorticotrophic hormone-independent Cushing's syndrome in a context of primary bilateral macronodular adrenocortical hyperplasia. While initial levels of cortisol were not very high, we could not manage to control hypercortisolism with ketoconazole monotherapy, and could not increase the dose due to side effects. The same result was observed with another steroidogenesis inhibitor, osilodrostat. The patient was finally successfully treated with a well-tolerated synergistic combination of ketoconazole and osilodrostat. We believe this case provides timely and original insights to physicians, who should be aware that this strategy could be considered for any patients with uncontrolled hypercortisolism and delayed or unsuccessful surgery, especially in the context of the COVID-19 pandemic.

## Learning points:

- Ketoconazole–osilodrostat combination therapy appears to be a safe, efficient and well-tolerated strategy to suppress cortisol levels in Cushing syndrome.
- Ketoconazole and osilodrostat appear to act in a synergistic manner.
- This strategy could be considered for any patient with uncontrolled hypercortisolism and delayed or unsuccessful surgery, especially in the context of the COVID-19 pandemic.
- Considering the current cost of newly-released drugs, such a strategy could lower the financial costs for patients and/or society.

## Background

Untreated or inadequately treated Cushing's syndrome (CS) is a morbid condition leading to numerous complications. The latter ultimately results in an increased mortality that is mainly due to cardiovascular events and infections. The goal of the treatment with steroidogenesis inhibitors is normalization of cortisol production allowing the improvement of comorbidities (1). Most studies dealing with currently available steroidogenesis inhibitors used as monotherapy reported an overall antisecretory efficacy of roughly 50% in CS.

Steroidogenesis inhibitors can be combined to better control hypercortisolism. To the best of our knowledge, we report here for the first time a patient treated with a ketoconazole–osilodrostat combination therapy.

## Case presentation

Here, we report the case of Mr D.M., 53-years old, diagnosed with adrenocorticotrophic hormone (ACTH)-independent CS 6 months earlier. At diagnosis, he presented with



resistant hypertension, hypokalemia, diabetes mellitus, easy bruising, purple abdominal striae and major oedema of the lower limbs.

## Investigations

A biological assessment was performed, and the serum cortisol levels are depicted in Table 1. ACTH levels were suppressed (mean levels 1 pg/mL). Mean late-night salivary cortisol showed a four-fold increase (Table 2), and mean 24 h-urinary cortisol showed a two-fold increase. Serum cortisol was 1000 nmol/L at 08:00 h after 1 mg dexamethasone dose at 23:00 h. The rest of the adrenal hormonal workup was within normal ranges (aldosterone: 275 pmol/L and renin: 15 mIU/L). An adrenal CT was performed (Fig. 1) and exhibited a 70-mm left adrenal mass (spontaneous density: 5 HU and relative washout: 65%) and a 45-mm right adrenal mass (spontaneous density: -2 HU and relative washout: 75%). The case was discussed in a multidisciplinary team meeting, which advised to perform 18F-FDG PET-CT and <sup>123</sup>I-Iodocholesterol scintigraphy before considering surgery. A genetic screening was performed, testing for ARMC5 and PRKAR1A pathogenic variants.

## Treatment

As this condition occurred during the COVID-19 pandemic, it was decided to first initiate steroidogenesis inhibitors to lower the patient's cortisol levels. Initially, ketoconazole was initiated and uptitrated up to 1000 mg per day based on close serum cortisol monitoring, with a three-fold increase of liver enzymes and poor control of cortisol levels (Table 1). In the absence of biological efficacy, ketoconazole was replaced by osilodrostat, which was gradually increased up to 30 mg per day (10 mg at 08:00 h and 20 mg at 20:00 h) without reaching normal cortisol levels (Table 1) and with slightly increased blood pressure levels. Considering the lack of efficacy of anticortisol drugs used as monotherapy, we combined osilodrostat (30 mg per day) to ketoconazole (600 mg per day), that is, at the last maximal tolerated dose as monotherapy of each drug.

## Outcome

This combination of steroidogenesis inhibitors achieved a good control in cortisol levels, mimicking a physiological circadian rhythm (Table 1D). The patient did not exhibit any side effect and the control of cortisol levels resulted in a rapid improvement of hypertension, kalemia, diabetes control and disappearance of lower limbs oedema. The patient underwent a <sup>18</sup>F-FDG PET-CT that did not exhibit any increased uptake in both adrenal masses and a <sup>123</sup>I-Iodocholesterol scintigraphy exhibiting a highly increased uptake in both adrenal masses, predominating in the left adrenal mass (70 mm). Unilateral adrenalectomy of the larger mass was then performed, and as the immediate post-operative serum cortisol level was 50 nmol/L, hydrocortisone was administered at a dose of 30 mg per day, with a stepwise decrease to 10 mg per day over 3 months. Pathological examination exhibited macronodular adrenal hyperplasia with a 70-mm adreno cortical adenoma (WEISS score: 1 and Ki67: 1%). The genetic screening exhibited a c.1908del p.(Phe637Leufs\*6) variant of ARMC5 (pathogenic), located in exon 5. The patient has no offspring and is no longer in contact with the rest of his family.

## Discussion

The goal of the treatment with steroidogenesis inhibitors is normalization of cortisol production allowing the improvement of comorbidities (1). Most studies dealing with currently available steroidogenesis inhibitors used as monotherapy reported an overall antisecretory efficacy of roughly 50% in CS. This rate of efficacy was probably underestimated in retrospective studies due to the lack of adequate uptitration of the dose; For example, the median dose reported in the French retrospective study on ketoconazole was only 800 mg/day, while 50% of the patients were uncontrolled at the last follow-up (2).

Steroidogenesis inhibitors can be combined to better control hypercortisolism. Up to now, such combinations, mainly ketoconazole and metyrapone, were mainly reported in patients with severe CS (median urinary-free

**Table 1** Serum cortisol levels at diagnosis (A), using ketoconazole monotherapy (B), using osilodrostat monotherapy (C) and using osilodrostat–ketoconazole combination therapy (D).

Serum cortisol (nmol/L)	08:00 h	24:00 h	16:00 h	20:00 h	12:00 h	16:00 h
A. At diagnosis	660	615	716	566	541	561
B. Ketoconazole monotherapy	741	545	502	224	242	508
C. Osilodrostat monotherapy	658	637	588	672	486	692
D. Osilodrostat–ketoconazole combination	436	172	154	103	135	274

**Table 2** Salivary cortisol levels at diagnosis (A), using ketoconazole monotherapy (B), using osilodrostat monotherapy (C) and using osilodrostat-ketoconazole combination therapy (D).

Salivary cortisol (nmol/L)	23:00 h	12:00 h	13:00 h	Mean
A. At diagnosis	47	62	38	49
B. Ketoconazole monotherapy	20	15	21	18
C. Osilodrostat monotherapy	85	90	56	77
D. Osilodrostat-ketoconazole combination	10	14	9	11

Cortisol (UFC) 30- to 40-fold upper-limit norm (ULN) and life-threatening comorbidities (3, 4). Normal UFC was reported in up to 86% of these patients treated with high doses of ketoconazole and metyrapone. Expected side effects (such as increased liver enzymes for ketoconazole or worsened hypertension and hypokalemia for metyrapone) were reported in the majority of the patients. The fear of these side effects probably explains the lack of uptitration in previous reports. Combination of steroidogenesis inhibitors has previously been described by Daniel *et al.* in the largest study reported on the use of metyrapone in CS; 29 patients were treated with metyrapone and ketoconazole or mitotane, including 22 in whom the second drug was added to metyrapone monotherapy because of partial efficacy or adverse effects. The final median metyrapone dose in patients controlled with combination therapy was 1500 mg per day (5).

Combination of adrenal steroidogenesis inhibitors should not be reserved to patients with severe hypercortisolism. In the case shown here, the association was highly effective in terms of secretion, using lower doses than those applied as a single treatment, but without the side effects previously observed with higher doses of each

treatment used as a monotherapy. To our knowledge, the association of ketoconazole and osilodrostat had never been reported. Ketoconazole blocks several enzymes of the adrenal steroidogenesis such as CYP11A1, CYP17, CYP11B2 (aldosterone synthase) and CYP11B1 (11-hydroxylase), leading to decreased cortisol and occasionally testosterone concentrations. Though liver enzymes increase is not dose-dependent, it usually happens at doses exceeding 400–600 mg per day (2). Osilodrostat blocks CYP11B1 and CYP11B2; a combination should thus allow for a complete blockade of these enzymes that are necessary for cortisol secretion. Short-term side effects such as hypokalemia and hypertension are similar to those observed with metyrapone, due to increased levels of the precursor deoxycorticosterone, correlated with the dose of osilodrostat (6). As for our patient, the occurrence of side effects should not lead to immediately switch to another drug, but rather to decrease the dose and add another cortisol-lowering drug. Moreover, considering the current cost of newly-released drugs such a strategy could lower financial costs for patients and/or society.

Another point to take into account is the current COVID-19 pandemic, for which, as recently detailed in experts' opinion (7), the main aim is to reach eucortisolism, whatever the way. Indeed patients presenting with CS usually also present with comorbidities such as obesity, hypertension, diabetes mellitus and immunodeficiency (8). Surgery, which represents the gold standard strategy in the management of CS (1, 9), might be delayed to reduce the hospital-associated risk of COVID-19, with post-surgical immunodepression and thromboembolic risks (7). Because immunosuppression and thromboembolic diathesis are common CS features (9, 10), during the COVID-19 pandemic, the use of steroidogenesis inhibitors appears of great interest. In these patients, combining steroidogenesis inhibitors at intermediate doses might allow for a rapid control of hypercortisolism without risks of major side effects if a single uptitrated treatment is not sufficient. Obviously, the management of associated comorbidities would also be crucial in this situation (11).

To conclude, we report for the first time a case of CS, in the context of primary bilateral macronodular adrenocortical hyperplasia successfully treated with a well-



**Figure 1**  
Adrenal CT depicting the bilateral macronodular adrenocortical hyperplasia.



tolerated combination of ketoconazole and osilodrostat. While initial levels of cortisol were not very high, we could not manage to control hypercortisolism with ketoconazole monotherapy, and could not increase the dose due to side effects. The same result was observed with another steroidogenesis inhibitor, osilodrostat. This strategy could be considered for any patient with uncontrolled hypercortisolism and delayed or unsuccessful surgery, especially in the context of the COVID-19 pandemic.

#### Declaration of interest

F C and T B received research grants from Recordati Rare Disease and HRA Pharma Rare Diseases. Frederic Castinetti is on the editorial board of Endocrinology, Diabetes and Metabolism case reports. Frederic Castinetti was not involved in the review or editorial process for this paper, on which he is listed as an author.

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#### Patient consent

Informed written consent has been obtained from the patient for publication of the case report.

#### Author contribution statement

V A was the patient's physician involved in the clinical care and collected the data. T B and F C supervised the management of the patient. F C proposed the original idea of this case report. V A drafted the manuscript. F C critically reviewed the manuscript. T B revised the manuscript into its final version.

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