Efficacy and tolerance of osilodrostat in patients with severe Cushing's syndrome due to non-pituitary cancers

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To the editor

Severe hypercortisolism (SH) is a rare life-threatening endocrine emergency, mainly caused by ectopic ACTH syndrome (EAS), which requires a rapid normalization of cortisol concentrations (1, 2). Due to their rapidity of action, steroidogenesis inhibitors, such as ketoconazole and metyrapone, given in monotherapy or in association, are recommended in this situation (1, 3, 4). Osilodrostat is a recently developed inhibitor of adrenal 11 β -hydroxylase (5) which has been shown to be effective, using a progressive titration of the drug dosage, in the treatment of Cushing's disease (5, 6, 7). Limited data are available on the use of osilodrostat in SH induced by EAS (8). Following the shortage of metyrapone in 2019, a temporary authorization for the use of osilodrostat was given by French authorities. We report herein our experience with osilodrostat in the treatment of three patients with severe Cushing's syndrome due to EAS and adrenal carcinoma (ACC).

Patient 1

A 51-year-old woman presented with a small cell lung carcinoma (SCLC) responsible for SH. She was effectively treated for 2 years by chemotherapy and 500 mg/day metyrapone after developing liver intolerance to ketoconazole. Following metyrapone shortage, 2 mg/day osilodrostat allowed control of cortisol levels. Recurrence of the SCLC was associated with an increase in plasma

cortisol to 1200 nmol/L. Osilodrostat dose was immediately increased to 5 mg/day for 4 days, and based on repeated plasma cortisol measurements, it was increased every 2–4 days in 5 mg/day steps. A maximal dose of 25 mg/day was reached after 2 weeks which allowed the mean plasma cortisol concentrations (determined from 3-day time samples) to be in the target range (200–500 nmol/L). Control of SH was sustained for 3 months until the death of the patient due to tumoral burden (Fig. 1A).

Patient 2

A 39-year-old man presented with an ACC responsible for SH (plasma cortisol=1495 nmol/L). Liver intolerance occurred after 10 days of ketoconazole treatment at 1200 mg/day. Osilodrostat was introduced at 5 mg/day together with mitotane 1500 mg/day. Based on repeated plasma cortisol measurements, osilodrostat was increased every 4–5 days by 4–5 mg/day steps. The maximal dosage of 44 mg/day was reached after 2 weeks and achieved normalization of plasma cortisol. To simplify anticortisol treatment during neoadjuvant anticancer chemotherapy, a block-and-replace (BAR) regimen was employed with osilodrostat 30 mg/day associated with hydrocortisone that was introduced when 08:00 h plasma cortisol started to decrease below normal (173 nmol/L). A high dosage (60 mg/day) of hydrocortisone was prescribed as required in patients treated with mitotane (9). Hypercortisolism was controlled for 4 months until surgical resection of the ACC (Fig. 1B).

Figure 1

Evolution of mean plasma cortisol concentrations in three patients treated with osilodrostat (A: patient 1; B: patient 2; C: patient 3). Cortisol values are the mean of 3-day time measurements. The shaded area corresponds to the normal range in our laboratory (200–500 nmol/L). The gray background steps represent the titration regimen of osilodrostat in mg/day. Arrow chemo: beginning of the second line antineoplastic chemotherapy. Arrow hepatitis: occurrence of liver intolerance to ketoconazole.

Patient 3

A 70-year-old man presented with a SCLC responsible for SH (plasma cortisol=1970 nmol/L) that was controlled with chemotherapy associated with metyrapone (750 mg/day) and ketoconazole (1200 mg/day). Following metyrapone shortage, osilodrostat was introduced at 1 mg/day, a dose that maintained the control of hypercortisolism, in association with ketoconazole (1200 mg/day). Recurrence of the SCLC was associated with an increase in plasma cortisol to 900 nmol/L. While ketoconazole treatment was continued, osilodrostat was

increased to 4 mg/day over 14 days, allowing a 50% decrease in cortisol concentration. A pharmacological interaction between chemotherapy (paclitaxel) and ketoconazole induced liver intolerance and all medications were stopped. After 1 week of drug withdrawal, plasma cortisol increased to 1200 nmol/L. Osilodrostat was reintroduced as monotherapy at 7 mg/day leading to control of SH in 7 days. Three weeks later, due to low cortisol concentrations (150 nmol/L, normal: 200–500 nmol/L), a 10 mg morning dose of hydrocortisone was prescribed in association with osilodrostat at 6 mg/day. This BAR regimen allowed reintroduction of anticancer chemotherapy and sustained control of hypercortisolism until the death of the patient 2 months later due to tumoral burden (Fig. 1C).

Discussion

These observations show that, using variable regimens, osilodrostat rapidly and safely controlled SH in three patients in whom metyrapone and ketoconazole could not be prescribed. The time to control of plasma cortisol concentrations was ≤ 2 weeks, and a maximal dose of 44 mg/day was used. The tolerance of osilodrostat was excellent: neither nausea nor changes in QTc or kalemia were observed. To date, we are only aware of one Japanese study (8) involving three patients with SH and EAS, who were treated in a phase 2 study using a fixed dose-titration protocol. Although the individual data were not provided, analysis of figures from this paper shows that osilodrostat normalized UFC in the short-term in approximately 5–9 weeks, that is, a significantly longer period than that observed in our patients. The precise dosage of osilodrostat was not specifically given, but in any case cannot be extrapolated to Caucasians, since the relative bioavailability of the drug is approximately 20% higher in Asian patients as compared to other ethnicities (5, 8).

In our series, osilodrostat controlled rapidly SH using a rapid increase in dosage that differs from that used in the Linc Studies (5, 6, 7) and the Japanese study (8). Our titration protocol was established based on the pharmacokinetics of osilodrostat, including a rapid absorption ($T_{max} \approx 1$ h), a half-life ≈ 4 h, and a steady state reached in 2 days (5). These data associated with those derived from animal studies, suggesting a dramatic decrease in plasma cortisol after at most 8 h following a single dose (10), which prompted us to use 2–5 days titration steps based on serial plasma cortisol measurements.

Osilodrostat was used using a BAR regimen in two patients, a therapeutic scenario which has not been previously described with this drug. The TID regimen and availability of various dosages for osilodrostat significantly reduced the number of steroidogenesis inhibitor pills to be taken (3, 4, 11, 12), a point that may favor patient compliance and be relevant in terms of quality of life. The BAR regimen may peculiarly be useful in a complex situation, such as SH in patients with non-pituitary cancers. Indeed, when antineoplastic therapy is effective on tumor burden, a condition that is usually evaluated by imaging after several weeks of delay, it may also induce a rapid concomitant decrease in cortisol which complicates the monitoring of drug dosage and requires repeated cortisol measurements. In our opinion, the BAR regimen with an effective drug that is associated with a low prevalence of drug-to-drug interactions (5) represents a valid therapeutic approach in these patients.

In conclusion, in a block-and-replace strategy aiming at controlling SH rapidly (13), and based on a limited number of observations, we suggest to start osilodrostat at a relatively high dosage, of at least 6 mg/day, when baseline cortisol levels are >1000 nmol/L; re-assess plasma cortisol (ideally associated with UFC) after 2–5 days for further adjustments and consider prescription of glucocorticoid replacement. Complementary observations in these complex therapeutic situations are needed to determine optimal starting doses of osilodrostat and duration of titration steps.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this letter.

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