Rapid control of severe ectopic Cushing's syndrome by oral osilodrostat monotherapy

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We read with great interest the recent letter by Haissaguerre *et al.* who used osilodrostat, a new 11 β -hydroxylase inhibitor, in three patients with Cushing's syndrome due to non-pituitary tumors (1). The reported cases had intense hypercortisolism with initial mean cortisol levels around 1400 nmol/L. No cases required to transfer to an intensive care unit (ICU). The substitution of previous inhibitors with osilodrostat, in combination with ketoconazole or mitotane in two patients, made it possible to control hypercortisolism. Severe Cushing's syndrome is a rare situation that can lead to death (2). The leading causes of mortality are dysmetabolic disorders such as profound hypokalemia uncontrolled diabetes, thromboembolic events, hypertension, cardiovascular diseases, severe infections, and acute psychiatric disorders (3). This critical situation requires emergency treatment and close monitoring. Several therapeutic strategies based on adrenal steroidogenesis inhibitors, such as metyrapone, ketoconazole, etomidate or mitotane can be used (4, 5, 6, 7). Bilateral adrenalectomy may be necessary as a rescue treatment in patients unresponsive to medical therapy (8). Osilodrostat was approved after clinical trials conducted on adults with Cushing's disease (9, 10). Its potential as a therapeutic against other causes of Cushing's syndrome remains to be evaluated. To justify its potential interest in severe Cushing's syndrome, we describe the cortisol response to osilodrostat as a first-line monotherapy on a 49-year-old woman admitted to the ICU (Fig. 1). Having read the letter by Haissaguerre, we decided to start osilodrostat with a high dose of 20 mg/day given the severe condition of our patient. To date, the literature on the efficacy of osilodrostat in Cushing's syndrome due to

non-pituitary tumors contains the letter by Haissaguerre (1) and a phase 2 study from Japan (11). A total of five ectopic Cushing's syndrome have been reported. None of them required intensive care, unlike our patient with a life-threatening presentation. This is probably the reason why in previous publications osilodrostat titration was performed every 2–5 days (1) or week (11). Normalization of cortisol levels was obtained after 15 and 44 days (1) or at least 4 weeks (11) for the five reported patients with ectopic Cushing's syndrome. Our patient required a more rapidly effective approach, which is why we chose to start with a high dose (20 mg/day) move quickly in 5 days to a block and replace strategy with the maximum recommended dose (60 mg/day). High dose osilodrostat as a first-line monotherapy normalized the cortisol levels of the patient in only 6 days, allowing a rapid discharge from ICU. ACTH levels remained elevated during osilodrostat treatment, demonstrating that the resolution of hypercortisolism was due to adrenal steroidogenesis inhibition.

A lower dose may have been sufficient, but we gave priority to a rapid decrease in cortisol levels, with the subsequent possibility to reduce osilodrostat as has been done with this patient. Among the rapidly effective options in ICU for severe Cushing's syndrome, etomidate may be used but an i.v. infusion is needed (6). Osilodrostat could be the first option to consider in severe Cushing's syndrome with the advantage of being given orally twice a day. Another option in severe Cushing's syndrome is a combined therapy with several anticortisol drugs (12). Our observation suggests that this combined strategy could be used as a second-line

Figure 1

Evolution of mean plasma cortisol concentrations for a severe ectopic Cushing's syndrome treated with a high dose of osilodrostat. Cortisol values are the mean of 6-day time measurements. The shaded area corresponded to cortisol reference ranges (200–550 nmol/L). The patient was hospitalized in ICU for 6 days due to profound hypokalemia and uncontrolled diabetes mellitus. The gray background steps represent the titration regimen of osilodrostat in mg/day. Rapid correction of hypercortisolism was followed by a complete blockage of cortisol production obtained with the maximum recommended dose in a 'block and replace' strategy. The initial high i.v. potassium intake and insulin dose declined in parallel with a slight delay. DOTATOC-⁶⁸Ga PET/CT performed on the 15th day revealed a pancreatic tumor (arrow) with liver metastases from a mixed neuroendocrine non-neuroendocrine tumor (MiNEN).

option in case of osilodrostat ineffectiveness after early cortisol monitoring.

In conclusion, high-dose osilodrostat was rapidly effective, easy to use and well tolerated, as a first-line monotherapy in an extremely severe Cushing's syndrome in ICU. As stated by Haissaguerre *et al.* complementary observations in these complex therapeutic situations are needed to determine optimal starting doses of osilodrostat and the optimal drug dosing schedule.

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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