Osilodrostat in Cushing’s disease: the management of its efficacy and the pitfalls of post-surgical results

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Summary
Osilodrostat is a novel, orally administered cortisol synthesis inhibitor, approved in 2020 by the European Medicines Agency (EMA) for the treatment of Cushing’s syndrome in adults. A significant amount of the studies currently available in the literature focus on treatment in patients with Cushing’s disease. However, data collected from patients treated with osilodrostat in real-life settings still represents a small entity. For this reason, in this article, we will discuss two real-life cases of patients with Cushing’s disease treated with this drug. The first report is about a 35-year-old woman with an adrenocorticotrophic hormone (ACTH)-secreting adenoma. After non-curative trans-nasal-sphenoidal (TNS) surgery, due to a small remnant of the adenoma, medical therapy with osilodrostat achieved fast and effective biochemical and clinical response. During treatment, progressive increase of ACTH levels and an enlargement of the pituitary remnant were documented, with planned radiosurgical treatment. The second case reports a 32-year-old man diagnosed with Cushing’s disease in 2020, who, after surgery refusal, started osilodrostat at progressively up-titrated doses, according to 24 h urinary free cortisol levels, up to 5 mg twice a day. With osilodrostat, the patient reached biochemical and clinical control of disease until TNS surgery in October 2021, with complete remission. The first post-surgical biochemical assessment was equivocal in spite of a transient clinical hypoadrenalism, reverted after 2 months with the restoration of physiological hypothalamic-pituitary-adrenal axis (HPA) function.

Learning points:
• Osilodrostat is a potent oral drug viable for Cushing’s disease as medical therapy when surgery is not feasible or remission cannot be reached.
• Osilodrostat proves to be a safe drug and its main adverse effect is hypoadrenalism, due to the adrenolytic action of the compound.
• Osilodrostat needs a very tailored approach in its clinical use because there is no correlation between the level of hypercortisolism pre-treatment and the dose required to reach disease control.

Background
Cushing’s disease is a clinical condition caused by an adrenocorticotrophic hormone (ACTH) secreting pituitary adenoma, which can lead to numerous clinical and biochemical alterations caused by an excessive endogenous cortisol secretion (1). The most common complications of hypercortisolism include hypertension, obesity, diabetes...
mellitus type 2, osteoporosis, capillary frailty and mood alterations.

According to the most recent consensus update on the diagnosis and management of Cushing’s disease, the first-line therapy is removing the pituitary adenoma via trans-nasal-sphenoidal (TNS) surgery (2, 3, 4). Surgery may achieve complete remission in up to 80% of patients with microadenomas and 60% of patients with macroadenomas (5, 6). Medical therapy for Cushing’s disease is suggested for the persistence of disease or recurrence after surgery and when surgery is not feasible; it can also be used in selected cases of severe disease to control cortisol concentrations before surgery (2). Medical therapy includes adrenal steroidogenesis inhibitors, somatostatin receptor ligands, dopamine agonists and glucocorticoid receptor antagonists.

Osilodrostat is a potent reversible 11β-hydroxylase inhibitor, recently approved in the United States for Cushing’s disease (FDA approval on 6 March 2020) and in Europe for endogenous Cushing’s syndrome (EMA approval on 9 January 2020) (2, 7).

A prospective double-blind phase III study (LINC 3), including 137 patients with persistent or recurrent Cushing’s disease, showed that, by week 34 of treatment, 86% of the patients randomly assigned to osilodrostat maintained normal urinary free cortisol (UFC) vs 29% in the placebo group, with also a significant decrease in body weight, blood pressure, total and LDL cholesterol, fasting plasma glucose and HbA1C concentrations and significant improvement of quality of life and depression scores. Most common adverse effects reported were related to the onset of hypocortisolism, mostly managed with dose titration or drug interruption (7). Of the patients, 42% documented adverse events potentially related to an increase in adrenal hormone precursors, including hypertension (≈10%) and hypokalemia (13%). Adverse events due to androgen excess were documented in ≈10% of female patients, but all these conditions were mild and did not cause study discontinuation. Transaminase elevation (>3× the upper level of normality (ULN)) was documented in only a few patients, all spontaneously reverted after dose adjustment. As for tumor size, a similar percentage of patients had either a decrease or an increase of the adenoma, whereas in patients with negative basal MRI, no evidence of a newly measurable pituitary tumor was reported. In the phase III multicenter trial LINC 4, published in March 2022, at week 12, 77% of patients in the osilodrostat arm reached a mean UFC below ULN vs 8% in the placebo group and 6/8 patients with severe hypercortisolism at diagnosis normalized cortisol levels during osilodrostat. Mean ACTH in the treatment group rose. At week 36, 59/73 patients (80.8%) had mean UFC ≤ ULN, with a persistent beneficial effect until the end of the follow-up at week 48 (79.5% complete response). The safety profile was confirmed favorable, with the most common adverse effects being reduced appetite, arthralgia and nausea. There was no correlation between the mean UFC at baseline and osilodrostat dose needed to reach normalized UFC levels (8). As such, osilodrostat has proved to represent a promising therapy for Cushing’s disease, achieving good biochemical control without significant adverse events (7, 8).

Nevertheless, real-life experience apart from the clinical trials setting is currently very limited and the heterogeneity of Cushing’s disease can lead to a variety of different clinical and biochemical responses. Therefore, the aim of this report is to share our clinical experience with osilodrostat, describing two different clinical scenarios that the endocrinologist can encounter in a real-life setting.

Case presentation

Case no. 1: A 35-year-old woman of Egyptian heritage was evaluated for hypercortisolism, in September 2020, due to depression and a 10 kg weight gain in the previous year. Blood and urinary tests showed elevated ACTH levels (101 pg/mL, vn 5–52 pg/mL) and 24 h UFC (4.1×, 5.6×, and 6.9× ULNr on 3 samples), loss of normal nocturnal suppression of cortisol and no suppression at the 1 mg overnight dexamethasone suppression test (DST 1 mg).

Case no. 2: A 32-year-old man was admitted to another hospital in 2020, complaining of fatigue and abdominal bloating progressively worsening since 2018. An HPA function assessment showed: 24 h UFC of 3.7–4× ULNr, mean ACTH 30.5 pg/mL and inadequate cortisol suppression after DST. Corticotropin-releasing hormone (CRH) test showed an ACTH (basal ACTH of 28.9 pg/mL, peak of 94.8 pg/mL with a +228%) and cortisol (basal: 13.92 µg/dL, peak: 24.18 µg/dL with a +74%) increase, suggestive of Cushing’s disease. Pituitary MRI was negative and no treatment was suggested. One year later, the patient was admitted to our hospital searching for a second opinion and being heavily symptomatic.

Investigation

Case no. 1: A CRH test showed a 47% ACTH increase and cortisol 90% suppression after 8 mg dexamethasone overnight test. Gadolinium-enhanced pituitary MRI...
highlighted a 9 mm microadenoma on the right side of the pituitary gland, contiguous to the sinus cavernous.

Case no. 2: Diagnosis of Cushing’s disease was confirmed (UFC: 2.39× ULNr, mean ACTH: 23.5 pg/mL). A new pituitary MRI highlighted a small hypointense 2–3 mm area in the anterior region on the left lobe of the gland.

**Treatment**

Case no. 1: A diagnosis of Cushing’s disease was done and the patient underwent endoscopic TNS surgery. The histological examination confirmed the diagnosis of ACTH-secreting pituitary adenoma (Ki67 < 1%). After surgery, the patient developed diabetes insipidus, was treated with desmopressin and showed no clinical improvement.

Biochemical evaluation showed the persistence of high ACTH and UFC levels (53.4 pg/mL and 24 h UF:C 13× ULNr, respectively), whereas MRI showed the persistence of a small remnant of the adenoma close to the cavernous sinus (Fig. 1).

Therapy with osilodrostat at the dose of 2 mg twice a day was started, and a follow-up every 15 days was scheduled.

Case no. 2: Because of the severe symptoms, the patient felt unfit to undergo neurosurgery, which was categorically refused, despite medical advice. Medical therapy with osilodrostat was started at a dose of 1 mg twice a day in March 2021 with every 15 days controls.

**Outcome and follow-up**

Case no. 1: At the first control, the patient was complaining of asthenia, headache and hypotension; 24 h UFC was, in two samples, respectively, 0.27× and 0.42× ULNr, in the lower part of the normality range and plasma cortisol at 08:00 h was 5.36 µg/dL. As such, the dose of osilodrostat was down-titrated at 1 mg a day, keeping 24 h UFC within the reference range and improving symptoms. Osilodrostat treatment at 1 mg/day maintained normal 24 h UFC levels for 6 months of follow-up, while ACTH levels progressively increased to 101 pg/mL. Clinical conditions of the patient continued to improve, depression resolved and she lost 8 kg. A control MRI performed 6 months after the beginning of treatment showed a marked increase of the tumoral remnant (Fig. 1).

After a multidisciplinary evaluation in February 2022, the patient has been scheduled for radiosurgery with a gamma-knife. In another MRI control in May 2022, the remnant was stable (Fig. 1). Meanwhile she is carrying on with 1 mg osilodrostat treatment.

Case no. 2: At the first follow-up visit, 24 h UFC levels were still 1.8× ULNr, so the osilodrostat dose was progressively up-titrated to 5 mg twice a day in June 2021, finally obtaining UFC normalization after 3 months, while ACTH levels progressively increased from 31.1 to 126 pg/mL. Clinical conditions of the patient markedly improved and the cushingoid phenotype disappeared; this clinical improvement convinced the patient to undergo surgery, after his initial skeptical approach.

In October 2021, the patient underwent TNS surgery still on 10 mg/day of osilodrostat: pathological tissue in the left portion of the pituitary was found and removed, and pituitary exploration did not show any other pathological tissue. IIC was positive for ACTH, prolactin and growth hormone.

After surgery, the patient was given the usual glucocorticoid replacement therapy (cortisone

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**Figure 1**

MRI of the sellar region, T1-weighted images in coronal section. From the left to the right: (A) March 2021, (B) November 2021 and (C) May 2022.
acetate 37.5 mg/day) for prevention of post-surgical hypoadrenalism. Irrespective of replacement therapy, the patient lamented asthenia. The first assessment of the HPA axis (evaluated off glucocorticoid treatment in the last 12 h) showed 08:00 h cortisol 12.5 µg/dL and ACTH 23 pg/mL, and normal remaining pituitary function. Cortisone acetate dose was tapered to 25 mg/day and a new evaluation performed 1 month later when the patient was off replacement therapy for 2 days showed normal 24 h UFC (ULNr 1.0×), ACTH 15 pg/mL and cortisol 15 µg/dL. Two months after surgery, a normal HPA axis function was proven (basal cortisol 12.1 µg/dL, peak after 1 µg ACTH stimulation test 19.4 µg/dL, vn >18 µg/dL; ACTH 39.4 pg/mL; 24 h UFC ULNr 0.86×). The patient showed a progressive amelioration of his phenotype and the disappearance of clinical symptoms for hypercortisolism; the follow-up pituitary MRI showed total removal of the adenoma and no evidence of pathological residual tissue.

Safety: In both patients, no changes in transaminase, electrolyte levels and blood pressure were documented and, apart from treatment-related hypoadrenalism, no other significant adverse effect was reported.

Discussion

This report describes two interesting clinical scenarios of Cushing’s disease treated with osilodrostat. In case no. 1, osilodrostat was used as medical therapy in a setting of persistence of disease after surgery, while in case no. 2, it was used as a ‘bridge therapy’ while waiting for a surgical solution.

Notably, in case no. 1, the lowest dose of osilodrostat rapidly normalized 24 h UFC, regardless of its very high starting levels. Such low dose of osilodrostat did not show any escape or tolerance phenomenon, maintaining a normal 24 h UFC throughout the first 12 months of follow-up. As also consistent with evidence from LINC 3, higher pre-treatment 24 h UFC levels did not necessarily require a higher dosage of osilodrostat to reach biochemical normalization (7). Concomitant with UFC decline, ACTH levels progressively rose during treatment, reaching the plateau level of 80–100 pg/mL, likely due to the drug-induced adrenal blocking, with a secondary effect on corticotroph pituitary cells. ACTH rise was expected and coherent with data reported in LINC 3, in which a significant increase in ACTH levels was documented from baseline to week 48 (18 pmol/L vs 50 pmol/L) (7). Whereas in LINC 3, no significant growth of the pituitary adenoma was reported in the treatment group, suggesting a substantial neutral role of osilodrostat on pituitary tumor growth; in this patient, a significant increase of the small tumor remnant was shown (7). So, we hypothesize that the observation period in the clinical trial was relatively short, and for longer periods of treatment, the continuous stimulating effect on pituitary corticotroph cells might exert a potential trophic role on the remnant of pituitary adenoma, as was documented in our case no. 1, in which when osilodrostat was started, there was an initial growth of tumor remnant paralleled with ACTH’s increase. Moreover, a 2021 case report described a case of rapid corticotroph tumor progression after 4 years of treatment with 10 mg/day of osilodrostat for persistent Cushing’s disease after transsphenoidal surgery, with residual tumor size increasing from 3 to 14 mm and ACTH levels from 73 to 500 pmol/L in a few months; this report also highlights the need for ACTH monitoring and periodical MRI controls during therapy with osilodrostat, which should become more frequent when ACTH levels have a steeper rise (9). LINC 4 data on pituitary tumors’ size showed a ≥20% size increase in 40% of patients and a ≥20% size decrease in 28% of patients at 48 weeks, with no clear pattern between treatment and tumor size timing, or with total osilodrostat dose (8). Further reports will be certainly necessary to better clarify and assess the real effect of osilodrostat on tumor growth.

In case no. 2, osilodrostat was able to normalize UFC levels in a pre-surgical setting. After TNS procedure, the first biochemical evaluation did not allow to assess disease remission. However, while the patient was complaining of weakness in spite of full glucocorticoid replacement therapy, which may have been suggestive of clinical remission of Cushing’s disease, biochemical evaluation showing fully normal cortisol and ACTH levels did not allow this conclusion, resembling physiological HPA axis function. A transient hypoadrenalism is common in patients with Cushing’s disease after curative surgery and depends on the inhibition of physiological ACTH secretion on normal pituitary cells by tumoral cells (10). In our patient, a possible contributing factor in the persistence of symptoms of hypoadrenalism even in glucocorticoid substitutive therapy might have been a persistent effect of osilodrostat even after therapy withdrawal. As such, in LINC 3, 10 of the 34 patients who were randomized to placebo after a 24-week period in osilodrostat kept UFC levels within the normal range also 8 weeks after therapy withdrawal (7). This long-lasting effect of osilodrostat cannot be fully explained by the reversible inhibitory effect on 11β-hydroxylase, and there
is no evidence supporting a permanent inhibition on adrenal function.

In addition, in our case, HPA function was completely restored after only 2 months from surgery, a rather short period compared to the median time described for Cushing’s disease. We can hypothesize that the prolonged and marked inhibition of cortisol secretion induced by pre-surgical treatment with osilodrostat from March to October 2021 may have reverted the pathological inhibition of normal corticotroph cells, thus reducing the post-surgical ‘stunning’ period of the HPA axis. This effect, however, makes it particularly difficult to evaluate the post-surgical state of disease, as ACTH levels might keep inappropriately high or normal right after surgery. As such, normalization of 24 h UFC and cortisol levels seem the best parameter to establish whether there is permanence or remission of the disease. We should emphasize that, while these processes might be theoretically possible, at the moment they remain purely putative due to small evidence available in the literature; more conclusive studies should assess the impact of pre-surgical osilodrostat therapy on post-surgical HPA axis recovery in Cushing’s disease.

Osilodrostat is affirming as one of the most effective and safe tools that the endocrinologist can use to successfully manage Cushing’s disease. The variability of Cushing’s disease is also evident in the heterogeneous response to the osilodrostat therapy in different patients. Osilodrostat needs a very tailored approach for every different patient, also due to the fact that baseline UFC levels are not predictive of osilodrostat dose necessary to control cortisol production. Predicting factors influencing response to therapy still need to be highlighted. The pre-operative use of such a potent cortisol synthesis inhibitor can lead to a substantial clinical and biochemical improvement of the patient, although it can be a caveat in evaluating the remission of Cushing’s disease after surgery. The most important element in the follow-up is represented by a periodical 24 h UFC dosage, the most effective strategy for dose titration. The possible effect of the osilodrostat therapy on the pituitary gland should be investigated more deeply.

For this reason, a wider variety of real-life reports will be fundamental to evaluate the efficacy of the drug and the problems linked to its use in a more diverse population.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

Author contribution statement
S Antonini, A Brunetti, B Zampetti, R C Cozzi were at the Endocrinology Department of ASST Grande Ospedale Metropolitano Niguarda, where the patients are currently being followed-up. D Boeris is at the Neurosurgery Department of the ASST Grande Ospedale Metropolitano Niguarda, where Case no. 1 was treated. A Saladino is at the Unit of Neurosurgery of the Fondazione IRCCS Istituto Neurologico Carlo Besta, where Case no. 2 was treated.

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