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Osilodrostat — an emerging drug for the medical management of Cushing's disease

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Abstract
Cushing's disease (CD) is a rare endocrine disorder characterized by the overproduction of adrenocorticotropic hormone (ACTH) by pituitary adenoma followed by hypercortisolaemia with severe complications. Although transsphenoidal resection of the defined pituitary adenoma has been the treatment of choice for the past decades, it does not always result in long-term remission — 10–30% of cases show ineffective surgical treatment or tumour recurrence even after initial success. Pharmacological therapies for cortisol reduction are often required for those who either cannot undergo pituitary surgery or when the surgery has failed, and patients still present with the persistent disease. Osilodrostat is a potent oral steroidogenesis inhibitor that has lately been shown as an effective adjuvant therapy in the management of patients with CD. In this article, we review the recent reports on the efficacy and safety of osilodrostat in clinical settings. **(Endokrynol Pol 2022; 73 (2): 371–374)**

Key words: *Cushing's disease; hypercortisolism; osilodrostat; steroidogenesis inhibitors; cortisol*

Introduction

Cushing's disease (CD) is the most common cause of endogenous hypercortisolaemia [1]. In normal physiology, adrenocorticotropic hormone (ACTH) is produced by the anterior pituitary and stimulates the steroidogenesis pathway in adrenal glands, which entails converting cholesterol to biologically active glucocorticoids, mainly cortisol. Steroid hormone biosynthesis is subjected to multiple regulatory mechanisms, which enable hormone production to be fine-tuned according to the current demands of the organism. However, this precise process is disrupted in CD patients because loss of negative feedback by the hypothalamic-pituitary-adrenal axis results in subsequent supraphysiological cortisol levels [2].

Cortisol excess is a potentially life-threatening condition leading to significant mortality, morbidity, and decreased quality of life. Patients with CD commonly develop metabolic complications such as dyslipidaemia, insulin resistance, prediabetes, and diabetes, along with hypertension and hypercoagulability, which overall result in increased mortality from cardiovascular disease compared to the general population [3–6]. Furthermore, central obesity with facial fat redistribution, skin changes, as well as depression and cognitive impairment reflect long-term physical and psychological abnormalities in patients with CD, which negatively affect the quality of life [3, 7].

Surgical treatment in Cushing's disease

The main therapeutic goal in CD patients is to decrease endogenous cortisol levels. Transsphenoidal surgery (TSS) is the treatment of choice and should be attempted in every patient due to promising remission rates (70–90%), and because it directly targets the underlying source of hypercortisolism, which is adrenocorticotrophic cell overgrowth [8]. Despite the initial efficacy, patients require long-term post-operative monitoring due to the relevant risk of recurrence [7, 9–12]. Collectively, relapse accounts for 15–66% among post-TSS patients with a median time of 5–10 years and is a major clinical challenge that needs to be addressed [7]. Medications can be utilized as adjunctive therapy when surgical has treatment failed to be curative, or as the first-line therapy for those reluctant to or ineligible for surgery.

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Overview of current medication strategies

Major pharmacological categories of medications for CD patients are pituitary-directed agents (pasireotide or cabergoline), adrenal steroidogenesis inhibitors (ketoconazole, metyrapone, mitotane), and glucocorticoid receptor antagonists (mifepristone) [13, 14].

Pasireotide is a multireceptor-targeted somatostatin analogue acting directly on autonomous corticotroph cells of pituitary adenoma, and it was the first FDA-approved drug to treat CD. Significant reduction and normalization of urinary free cortisol (UFC) have been reported in patients treated with twice-daily short-acting pasireotide as well as once-monthly long-acting pasireotide in two multicentre phase III studies [15, 16]. However high rates of adverse effects including deterioration of pre-existing diabetes or hyperglycaemia and elevated haemoglobin A1c in previously non-diabetic patients were reported in both clinical trials. Thus, the induction of diabetogenic effects can be a substantial problem related to pasireotide pharmacotherapy [17, 18].

Ketoconazole and metyrapone are adrenal steroidogenesis inhibitors that have been approved for the treatment of CD in Europe and are commonly used "off label" for that purpose in the USA [14]. Although ketoconazole has been shown to rapidly induce normalization of cortisol secretion with consequent improvement in the clinical picture, it also inhibits androgen synthesis and may lead to liver damage [19, 20]. Levoketoconazole, the stereoisomer of ketoconazole, is another new alternative in the management of CD. In a recent phase III study, 30% of patients were reported to have normalization of UFC through the 6-month treatment [21, 22]. Due to these initial promising results, the FDA recently accepted for review the application for levoketoconazole in the treatment of CD. However, more time is needed to compare its safety profile with ketoconazole [23].

Metyrapone treatment can lead to hypertension and hirsutism due to the accumulation of mineralocorticoid precursors and adrenal androgens [20]. Mifepristone acts as the glucocorticoid receptor antagonist and has been Food and Drug Administration (FDA) approved for treating hyperglycaemia in CD patients with secondary diabetes. However, due to its abortifacient properties, it should be avoided in women of childbearing age [7].

In light of the unmet medication need for the optimal treatment of patients with CD, the FDA and the European Medicines Agency (EMA) approved osilodrostat as a novel therapeutic agent [24]. Herein we describe the recent studies assessing the safety profile and efficacy of osilodrostat in clinical settings.

Osilodrostat in clinical trials

Phase I and II studies

Osilodrostat is a potent inhibitor of 11-β-hydroxylase and aldosterone synthase enzymes, which catalyse the final steps of cortisol and aldosterone synthesis in adrenal steroidogenesis [25]. Due to its prevalent action on the mineralocorticoid pathway, osilodrostat was initially evaluated as an antihypertensive drug. Phase I studies on healthy subjects indicated that osilodrostat administration was associated with decreased urinary and plasma aldosterone levels. Moreover, a decrease of baseline and ACTH-stimulation cortisol secretion was observed [26, 27]. Based on these preliminary reports, osilodrostat was further investigated in trials including hypertensive patients, which confirmed its suppressive effect on ACTH-stimulated cortisol response [28].

Two open-label, multicentre phase II trials were conducted to evaluate the safety and efficacy of osilodrostat in patients with CD [29, 30]. In the first multicentre clinical trial (LINC 1 study), osilodrostat was orally administered to 12 patients with recurrent CD after pituitary surgery and 24-hour mean urinary free cortisol (mUFC) $\geq 1.5 \times$ upper limit of normal (ULN). All 12 of the participants successfully completed the 10-week phase I experiments with good tolerance of osilodrostat. As a result of treatment, normalization of mUFC was achieved among 11 patients, and 1 patient experienced a reduction of at least 50% mUFC [29]. The second, follow-up trial (LINC 2) further assessed osilodrostat in patients with CD over a longer period. In this study, patients were treated for 22 weeks, and 15 out of 19 (78.9%) had normal mUFC levels by the end of the study. Morning serum and salivary cortisol decreased to normal levels whereas late-night salivary cortisol levels remained elevated during the treatment [30].

Phase III studies

In 2020, Pivonello et al. reported the efficacy and safety of osilodrostat in a multicentre phase III study (LINC 3) that included a double-blind, randomized withdrawal phase, which resulted in the FDA approval of osilodrostat in the treatment of CD [24].

The 48-week study was conducted among 137 patients and consisted of four study periods. 87.6% of patients had prior TSS surgery and had persistent or recurrent CD because of unsuccessful pituitary surgery, whereas 75% of CD patients had previously received pharmacological therapy. The primary endpoint, measured at the end of the withdrawal period (at the 34th week — 3 study period), was a proportion of complete responders in terms of mUFC $\leq$ ULN. Within the first 24 weeks a drug titration was done to identify the effective

osilodrostat dose, and once the dose was determined at the end of week 12 (1 study period) treatment was continued until week 24 (2 study period). Out of 137 enrolled patients, 71 (51.8%) met the predefined criteria of mUFC ≤ ULN at week 24 without any dose increases after week 12; therefore, those participants were eligible to undergo randomization withdrawal. At week 26, double-blinded study period 3 began, in which 36 and 35 patients were assigned to treatment and placebo groups, respectively, and continued the treatment for 8 weeks until week 34. The primary efficacy endpoint was met because the complete response rate of the treatment group was statistically significantly different compared to the placebo group (86% *vs.* 29% had mUFC < ULN). It was reported that osilodrostat was significantly superior to the placebo in maintaining UFC normalization [24].

The study was followed by an open-label extension period (study period 4) until week 48. Patients requiring a dose increase and those who failed to meet the predefined criteria (with mUFC 1.5 × > ULN) throughout previous study periods were labelled as nonresponders and assigned to study period 4 with responders from study period 3. 66% of all enrolled participants had controlled mUFC at the end of the week 48, and their complete response rate improved. Within the first 12 weeks, the most evident clinical and laboratory response was observed and generally remained stable throughout the following weeks of the study. The mean daily dose of osilodrostat was 11 mg/day, and the median time to first complete response was 41 days. Clinical response was evaluated with cardiovascular-related metabolic parameters associated with hypercortisolism such as weight, BMI, glucose, blood pressure and total cholesterol, and health-related quality of life measures (CushingQoL and Beck Depression Inventory scores), which improved considerably from baseline [24, 31].

As a consequence of the promising initial results of the study, the FDA approved osilodrostat in treating CD patients, although an additional phase III study period had to be completed because 8 weeks was considered too short to determine the long-term efficacy and safety of osilodrostat compared with placebo [24, 32]. To confirm the results from Pivonello et al., a 48-week safety and efficacy, multicentre, randomized, double-blind phase III study was designed (LINC 4) [33]. In this trial, osilodrostat was compared with placebo for 12 weeks, after which all patients received osilodrostat for an additional 36 weeks. The study included 73 patients, who were randomized in a 2:1 ratio (osilodrostat or placebo). The primary endpoint was the percentage of participants achieving a complete response (mUFC < ULN) at 12 weeks. The complete results from the LINC 4 trial have not been published yet, and therefore only limited data are available. However, the initial reports have indicated that patients treated with osilodrostat achieved a statistically significant higher rate of complete response compared with the placebo group [33].

Safety of osilodrostat

The most common adverse effects (occurring in > 25% of patients) associated with osilodrostat treatment reported in the clinical trials were decreased appetite, nausea, fatigue, arthralgia, and headache [24, 33]. Adrenal insufficiency was reported in 28% of LINC-4 trial participants. Hypocortisolism occurred in 51% of patients, and adverse events related to adrenal hormone precursors were found in 42% of study participants [33].

Because osilodrostat might have a dose-dependent effect on QT interval prolongation, patients with additional risk factors for QT prolongation require close monitoring during therapy. Moreover, because osilodrostat potentially leads to hypokalaemia, careful observation of the potassium levels should be performed in the clinical follow-up of patients receiving osilodrostat [24, 32]. Additionally, osilodrostat potentially increases testosterone levels, thereby causing hirsutism and acne in female patients. Other, rare adverse effects associated with osilodrostat therapy are urinary tract infections, nasopharyngitis, and neutropaenia [24, 32].

Overall, osilodrostat is generally well tolerated and seems to have a good safety profile, which may positively impact treatment compliance. Moreover, a recent meta-analysis showed superiority of osilodrostat over other medications in CD [34].

Can osilodrostat improve the treatment outcomes in the population of Polish patients with persistent hypercortisolaemia?

Treatment of patients with persistent CD and hypercortisolaemia in Poland is challenging, primarily due to restricted production of ketoconazole and the lack of reimbursement for steroidogenesis inhibitor therapies. As a result, available therapeutic strategies are highly limited, and many CD patients are not provided with the adequate treatment. Osilodrostat may prove beneficial in the management of CD in Polish patients, especially in those who do not respond or cannot tolerate currently available therapies. Thus, future studies assessing the clinical outcomes of osilodrostat treatment in the Polish population of patients with CD are warranted.

Conclusions

Cushing's disease is a life-threatening endocrine disorder associated with increased morbidity and

mortality and decreased quality of life due to its serious clinical burden. Recent clinical trials have proven the efficacy of osilodrostat, an oral steroidogenesis inhibitor, in the treatment of recurrent CD. In particular, osilodrostat treatment has been associated with rapid UFC normalization and sustained clinical improvement. Osilodrostat therapy was well-tolerated throughout the clinical trials, although adverse effects including adrenal insufficiency, nausea, hypokalaemia, or QT prolongation were noted. Additional long-term studies will provide further information on the efficacy and safety of osilodrostat for the treatment of CD.

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