Drug Design, Development and Therapy

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REVIEW

Clinical Utility of Osilodrostat in Cushing's Disease: Review of Currently Available Literature

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Abstract: Cushing's disease (CD) is caused by endogenous hypercortisolism as a result of adrenocorticotropin (ACTH) secretion from a pituitary tumor. The condition is associated with multiple comorbidities and increased mortality. First-line therapy for CD is pituitary surgery, performed by an experienced pituitary neurosurgeon. Hypercortisolism may often persist or recur after initial surgery. Patients with persistent or recurrent CD will generally benefit from medical therapy, often administered to patients who underwent radiation therapy to the sella and are awaiting its salutary effects. There are three groups of medications directed against CD, including pituitary-targeted medications that inhibit ACTH secretion from tumorous corticotroph cells, adrenally-directed medications that inhibit adrenal steroidogenesis and a glucocorticoid receptor (GR) antagonist. The focus of this review is osilodrostat, a steroidogenesis inhibitor. Osilodrostat (LCI699) was initially developed to lower serum aldosterone levels and control hypertension. However, it was soon realized that osilodrostat also inhibits 11-beta hydroxylase (CYP11B1), leading to a reduction in serum cortisol levels. The focus of drug development then shifted from treatment of hypertension to treatment of hypercortisolism in CD. In a series of studies (LINC 1 through 4), osilodrostat was shown to be effective in normalizing 24-h urinary free cortisol (UFC) in the majority of treated patients and was approved for patients with CD who have failed surgery or are not surgical candidates. Further study is needed to examine the role of combination therapy as well as long-term outcomes of treated patients. Osilodrostat was shown to have an overall good safety profile. Most common adverse effects include nausea, headache, fatigue, arthralgias, dizziness, prolonged QT_c interval, hypokalemia. In females, the drug can cause hirsutism and acne. Osilodrostat is administered twice daily, making it a good choice for patients with difficulty adhering to more complex regimens. Osilodrostat has an important, albeit adjunctive, role in the management of patients with CD.

Keywords: Cushing's disease, Cushing's syndrome, osilodrostat, LCI699, pituitary adenoma, steroidogenesis inhibitor, medical therapy

Introduction

Endogenous Cushing's syndrome (CS) is caused by pathological hypercortisolism and can be adrenocorticotropin (ACTH)-dependent (80%) or ACTH-independent (20%). The most common cause of ACTH-dependent CS is a pituitary corticotropinoma [Cushing's disease (CD)], which secretes ACTH autonomously and drives excessive cortisol secretion by the adrenal glands. Less frequently, the source of cortisol production is ACTH-independent and arises from adrenal gland lesions, including adrenal adenoma, hyperplasia or carcinoma.[1,2]

Common clinical features of CS/CD are rounded ("moon") facies with disproportionate supraclavicular and dorsocervical fat deposition, muscle loss from arms and legs, thin skin with easy bruising and wide, violaceous striae. In addition, CS/CD is often associated with visceral obesity, hypertension, hyperlipidemia, diabetes mellitus, osteoporosis, myopathy, increased risk of infection and cardiovascular complications as well as a variety of mood and behavioral manifestations. Patients with CS/CD have increased morbidity and mortality, especially from cardiovascular disease.[3]

First-line therapy for CD is transsphenoidal surgery by an experienced pituitary neurosurgeon, aimed at selectively resecting the underlying pituitary adenoma. Despite appropriate surgery, there is frequent tumor recurrence. As

Received: 14 February 2023
Accepted: 20 April 2023
Published: 27 April 2023

a corollary, many patients require additional therapy, including radiation therapy to the sella with interim medical therapy, medical therapy alone, or bilateral adrenalectomy.

Patients who are not candidates for surgery may benefit from medical therapy to control their disease. Patients with persistent disease despite surgery (20–30%) or recurrent disease (20–35%), which may occur many years after surgery, are also candidates for medical therapy.[4] Indeed, data suggest that 20–35% of patients in remission will relapse within 10–15 years.[5] Patients with severe hypercortisolism may also need to be treated medically in order to optimize their medical status preoperatively. These include patients with serious infections, recent ischemic cardiovascular events or acute psychosis, all of whom are candidates for medical therapy, until they are stable enough to undergo surgical resection of the underlying tumor.[2]

Currently available medications for the treatment of CD can be divided in three groups, including pituitary-targeted medications, adrenally-directed medications (inhibitors of cortisol synthesis), and a glucocorticoid receptor (GR) antagonist.[1]

Pituitary-targeted medications inhibit ACTH secretion from corticotroph adenoma cells. Currently available pituitary-directed medications include a somatostatin receptor ligand (pasireotide) and a dopamine agonist (cabergoline).

Pasireotide activates somatostatin receptor subtypes 1, 2, 3, and 5. In particular, activation of type 2 and type 5 receptors is thought to play an important role in the inhibition of pituitary ACTH secretion.[3] Pasireotide may also induce shrinkage of corticotroph pituitary adenomas. Pasireotide can be administered subcutaneously twice daily, owing to its half-life of 12 hr. In addition, a long-acting formulation, pasireotide long-acting release (LAR), is available and is administered once monthly as an intramuscular injection, which can improve adherence to therapy.[3] Hyperglycemia/diabetes mellitus is a common adverse effect. As a corollary, glucose levels should be closely monitored in patients with or without preexisting diabetes mellitus. Hyperglycemia occurs as a consequence of inhibition of insulin and incretin secretion and resolves after stopping therapy.[5]

Cabergoline, a dopamine agonist, is used "off-label" as treatment of CD. Dopamine receptors (D2) are expressed in tumorous lactotrophs, thereby accounting for the drug's efficacy in patients with prolactinomas. In addition, D2 receptors are often present in tumorous corticotrophs, suggesting that cabergoline may be effective in reducing ACTH secretion in patients with CD.[3] Cabergoline can be effective in controlling hypercortisolism in approximately 30% of patients with CD.[5] Cabergoline is administered orally and can be effective when administered less often than daily, owing to its long plasma half-life and extensive enterohepatic circulation. Overall, the drug has a favorable safety profile. In addition to controlling hypercortisolism, cabergoline may cause shrinkage of pituitary tumors.[3]

Adrenally-directed medications are steroidogenesis inhibitors that inhibit one or more steps involved in cortisol synthesis. Currently available agents include ketoconazole, levoketoconazole, metyrapone, osilodrostat, mitotane, and etomidate. Of note, use of ketoconazole, metyrapone, mitotane, or etomidate in patients with CD is "off label" in the US.

Ketoconazole is generally a good choice in female patients with CD, since it may improve hirsutism and menstrual cycles. By controlling hypercortisolism, ketoconazole therapy may result in several possible clinical benefits, including improvements in blood pressure, glucose metabolism, body weight, and psychiatric symptoms. The most concerning side effect is liver toxicity, which can be severe and life-threatening. The drug should be avoided in patients with severe liver disease. Levoketoconazole is a ketoconazole enantiomer, which has higher potency when compared to racemic ketoconazole, and is administered twice daily. In contrast, ketoconazole has to be administered 3 times daily in most patients.

Metyrapone is often a better choice in male patients with CD, owing to its androgenic effects (acne and hirsutism) in females. It has similar clinical benefits to ketoconazole. However, serum potassium levels should be followed closely, as the drug may cause hypokalemia.[6] Metyrapone was discovered in 1950s and is still widely used. Metyrapone is administered 3–4 times daily, thereby posing challenges for adherence to therapy.[6]

The only currently available GR antagonist is mifepristone. Although clinically effective in ameliorating the consequence of hypercortisolism in CD, cortisol levels do not decrease on mifepristone therapy, thereby necessitating dose titration based on clinical parameters. Patients on mifepristone therapy need to be monitored for low potassium levels and QT_c prolongation. Endometrial thickening and metrorrhagia may occur in women. Patients with hypokalemia may benefit from the addition of potassium-sparing, mineralocorticoid receptor antagonists, including spironolactone or eplerenone.[7]

Clearcut indications for combination medical therapy have not yet been established in CD. Prior studies suggest that combination therapy may be used in patients with severe hypercortisolism and may avert the need for bilateral adrenalectomy. However, further studies are needed to clarify the group of patients who will benefit the most from combination therapy.[2]

The aim of this review is to discuss data on osilodrostat, a relatively novel steroidogenesis inhibitor. Osilodrostat (Isturisa™) has been developed by Novartis; however, Recordati acquired all rights to osilodrostat in July 2019.[8] Osilodrostat was previously known as LCI699 during clinical development.

Osilodrostat has been approved by the European Medicines Agency (EMA) on January 9, 2020, and by the Food and Drug Administration (FDA) on March 6, 2020, for the treatment of patients with CS (EMA) or CD (FDA) who are not candidates for pituitary surgery or those who have failed surgery.[8,9]

Methods

In order to identify the primary literature used to compile this review article, we conducted electronic literature searches using PubMed and the keywords osilodrostat, LCI699, Cushing's syndrome, Cushing's disease, steroidogenesis inhibitor, medical therapy. In addition, the reference lists of articles that were retrieved were manually searched in order to identify additional references. Articles were cited at the authors' discretion.

Historic Perspectives, Discovery, and Early Drug Development

Interestingly, osilodrostat (LCI699) was not originally developed as a medication for CD. The drug (LCI699) is a derivative of fadrozole, a non-steroidal aromatase inhibitor used in Japan as treatment of patients with breast cancer. In early stages of drug development, osilodrostat (LCI699) was studied as a possible therapy for patients with hypertension and primary aldosteronism. Approximately 10% of hypertensive patients have primary aldosteronism, which is caused by autonomous aldosterone overproduction by one or both adrenal glands. It is very important to treat primary aldosteronism appropriately in order to mitigate excess cardiovascular morbidity and mortality.

LCI699 was the first oral inhibitor of aldosterone synthase (CYB11B2) developed for human use. Based on in vitro data, the drug was reported to inhibit aldosterone synthase (IC_{50}: 0.7 nM) and 11 beta hydroxylase (CYP11B1), albeit with a higher IC_{50} (2.5 nM) (Figure 1).[10]

In a Phase I trial conducted in healthy volunteers, LCI699 administration in multiple doses for up to 7 days led to a decrease in plasma and urine aldosterone but no change in serum cortisol levels.[11]

In a Phase II trial, LCI699 was administered to 14 patients with primary aldosteronism for up to 4 weeks (in doses up to 1 mg twice daily).[12] Decreases in plasma and urine aldosterone were reported with no change in unstimulated cortisol levels. However, a decreased cortisol response to cosyntropin was noted at the end of the study period, resulting from partial inhibition of CYP11B1.

In other phase II clinical trials, LCI699 was administered to patients with essential or resistant hypertension in doses up to 1 mg daily and was found to result in a lower blood pressure response in comparison with standard doses of eplerenone (50 mg twice daily).[13,14] Again, cortisol response to cosyntropin stimulation was blunted. Thus, the effects of LCI699 on inhibition of cortisol synthesis were recognized and the interest shifted towards developing the drug as a potential treatment for CD.[15–17]

Preclinical Data (Animal and in vitro Studies)

Pasireotide inhibits ACTH secretion from the pituitary gland and osilodrostat inhibits adrenal steroidogenesis, resulting in decreased cortisol secretion from the adrenal glands. These two medications were studied in animals to assess their safety profile, efficacy, and toxicity. A total of 120 Wistar rats were selected to receive pasireotide monotherapy, osilodrostat monotherapy, or various doses of osilodrostat/pasireotide combination therapy.[18] Rats were followed for 13 weeks. Osilodrostat monotherapy was associated with hypertrophy of adrenal glands, liver, and ovary, as well as increased mean body weight gain in female rats. On the other hand, pasireotide monotherapy and combined therapy resulted in a reduction in mean body weight gain. Overall, both osilodrostat and pasireotide monotherapy and osilodrostat/pasireotide in combination were found to have acceptable safety profile in rats.[18]

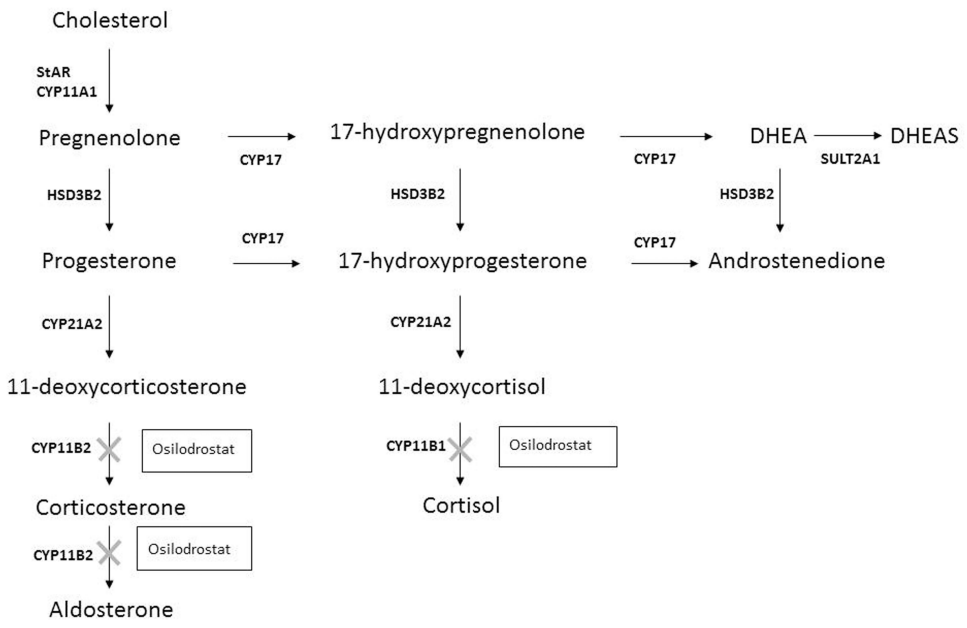

Figure 1 Outline of adrenal steroidogenesis, showing the sites of action of osilodrostat.
Abbreviations: CYP11A1, cholesterol side-chain cleavage enzyme; CYP11B1, steroid 11 beta hydroxylase; CYP11B2, aldosterone synthase (steroid 18 hydroxylase); CYP17, steroid 17 alpha hydroxylase/17,20 lyase; CYP21A2, steroid 21 hydroxylase; HSD3B2, 3 beta hydroxysteroid dehydrogenase/delta (5)-delta (4) isomerase; StAR, steroidogenic acute regulatory protein; SULT2A1, steroid sulfotransferase.

In an in vitro study, human adrenocortical cell cultures were incubated with osilodrostat, metyrapone, or ketoconazole. Cortisol and ACTH levels were measured by immunoassay. Results showed that osilodrostat inhibited cortisol and aldosterone secretion more potently than metyrapone (2 times more potently) and ketoconazole (18 times more potently). The metyrapone dosage required to achieve normal 24 hr urinary free cortisol (UFC) in vivo is significantly higher than that of osilodrostat, which is explained by differences in pharmacokinetics and pharmacodynamics between the 2 drugs.[19]

Pharmacokinetics/Pharmacodynamics (Phase I, II) – LINC 1 and 2

Osilodrostat acts by inhibiting two enzymes. The first enzyme is 11-beta-hydroxylase (CYP11B1), which catalyzes the final step in cortisol synthesis; enzyme inhibition reduces the conversion of 11-deoxycortisol into cortisol. The second enzyme is an 18-hydroxylase (CYP11B2) which directly results in aldosterone synthesis; enzyme inhibition blocks the conversion of 11-deoxycorticosterone into aldosterone.[8,9,20,21] As mentioned above, osilodrostat was initially developed as a potential antihypertensive agent in patients with essential hypertension or those with primary aldosteronism, owing to its effects on the mineralocorticoid pathway. However, osilodrostat was found to have limited efficacy in hypertensive patients while it decreased cortisol levels, thereby shifting the interest towards its development as a potential treatment of CD.[22]

Osilodrostat has a longer half-life (4 h) than metyrapone (2 h) and has a higher potency than metyrapone in inhibiting 11-beta-hydroxylase in vitro.[21] Osilodrostat is mostly excreted in the urine (91%). Studies have shown that co-administration of osilodrostat with oral combined contraceptives does not change the pharmacokinetics of contraceptive agents.[20]

Several clinical studies were conducted to evaluate the efficacy and safety of osilodrostat in CD in humans (Table 1). LINC 1 represents a 10 week, multicenter, proof-of-concept study including only 12 patients.[23] The purpose of this study was to show that LCI699 can successfully decrease UFC levels in patients with CD (baseline mean UFC: 4.7 times above the upper normal limit) and assess drug safety. At the end of the treatment period, 11 out of 12 patients had normal UFC levels. In addition, LCI699 treatment was well-tolerated with an overall reassuring safety profile.[23]

LINC 2 represents a phase II open label, prospective study of two patient cohorts, including a follow-up and an expansion cohort. The follow-up cohort included four patients previously involved in the LINC 1 study, who did not achieve UFC normalization. The initial osilodrostat dose ranged between 4 and 20 mg/day and was the maximal tolerable

dose in the LINC 1 study. The expansion cohort included 15 new patients with CD and UFC more than 1.5 times above the upper normal limit. A total of 19 patients were followed for 22 weeks.[24] At 10 weeks, 84.2% of patients achieved normal UFC and at 22 weeks, 78.9% achieved normal UFC. Adverse effects included diarrhea, nausea, adrenal insufficiency, and new or worsening hirsutism in females. Osilodrostat was overall well-tolerated with a good safety profile.[21,24] These studies paved the way for confirmatory, phase III studies (LINC 3 and LINC 4), which evaluated the efficacy and safety of osilodrostat in larger study populations (Table 1).

Phase III (LINC 3 and 4) – Clinical Efficacy and Safety

Osilodrostat was further studied in two phase III studies (LINC 3 and LINC 4).

LINC 3 was a multicenter, double-blind, randomized, drug withdrawal phase study, which was published in 2020.[25] The study assessed the efficacy and safety profile of osilodrostat versus placebo during a drug withdrawal phase.[25]

The study took place between November 2014 and March 2017, during which a total of 202 patients were screened and 137 subjects were enrolled to receive open-label osilodrostat during study period 1 (weeks 1–12). The median age of participants in the study was 40 years, and 77% of study subjects were female. Many of the patients enrolled in the study were previously on pasireotide, cabergoline, mifepristone, metyrapone, and mitotane before enrollment. Patients who received prior therapies were eligible to enroll in the study after an appropriate washout period, depending on the treatment they had previously received, including 1 week for steroidogenesis inhibitors, 4 weeks for dopamine agonists, 4 weeks for mifepristone, 1 week for short-acting pasireotide, 8 weeks for long-acting pasireotide, or 6 months for mitotane.[25] Osilodrostat dose was adjusted every 2 weeks until UFC levels normalized. In study period 2 (weeks 13–

Table 1 Data from the LINC Studies Examining the Efficacy and Safety of Osilodrostat in Patients with Cushing's Disease

	Number of Patients	Study Duration (Weeks)	Study Design	Efficacy (Primary Endpoint)	Safety Data (Most Common Side-Effects)
LINC 1	12	10	Proof of concept	91.6% achieved normal UFC	Fatigue (58%), nausea (42%), headache (25%), diarrhea (25%), hypokalemia (25%), arthralgia (17%), dizziness (17%)
LINC 2	19 (4 from LINC 1 study, 15 new patients)	22	Phase II open label, prospective study, including follow up (4 pts) and expansion cohort (15 pts)	78.9% achieved normal UFC	Nausea (32%), diarrhea (32%), fatigue (32%), adrenal insufficiency (32%)
LINC 3	137 130 35 vs 36	1–12, Phase 1 13–24, phase 2 26–34, Phase 3	Open-label (phase 1 and 2) Double-blind, randomized withdrawal, placebo-controlled (phase 3; 35 patients on osilodrostat vs 36 patients on placebo)	53% achieved normal UFC without dose uptitration (phase 2) 86% achieved normal UFC vs 29% with placebo (phase 3)	Nausea (42%), headache (34%), fatigue (28%), adrenal insufficiency (28%), hypokalemia (13%), hypertension (12%), hirsutism (females: 9%), acne (females: 8%), prolonged QTc (4%)
LINC 4	73 106	12 + 36 (total: 48) 72	Randomized, double-blind, placebo-controlled, multicenter; followed by open-label osilodrostat for 36 weeks Extension phase	77% achieved normal UFC with osilodrostat vs 8% with placebo after 12 weeks 81% achieved normal UFC by week 72	Decreased appetite (45%), arthralgias (45%), fatigue (38%), nausea (37%), headache (33%), myalgia (26%), dizziness (26%), adrenal insufficiency (25%), increased serum testosterone (25%)

Note: Osilodrostat was administered at dosages between 4–100 mg (LINC 1) and 4–60 mg (LINC 2, 3, 4).
Abbreviation: UFC, 24 hr urinary free cortisol.

24), a total of 130 patients received their previously established dose of osilodrostat.[9] During this phase, 53% of patients achieved normal UFC without dose up-titration between weeks 13–24.[25]

Study period 3 lasted between weeks 26–34. At 26th week, there was a double-blind, randomized withdrawal, placebo-controlled phase, during which patients were randomly assigned to receive either osilodrostat or placebo. A total of 35 patients were assigned to receive osilodrostat and a total of 36 patients received placebo. Prior to withdrawal phase, the dose of osilodrostat was adjusted for each participant individually based on UFC levels and the median dose was 10 mg per day, with the mean peak dose of 17.8 mg/day. The randomized withdrawal phase lasted until the 34th week. At the end of this phase, 86% (31 of 36) of subjects on osilodrostat achieved a complete response versus 29% (10 of 34 patients) of those on placebo, which was a statistically significant difference ($p < 0.0001$). The average time to UFC normalization was 41 days and at least 66% of patients maintained normal UFC levels 6 months after initial response.[21,25] In the LINC 3 study, 4% of patients showed an increase in ALT or AST on osilodrostat treatment.[26]

LINC 4 was a randomized, double-blind, placebo-controlled, multicenter study of 73 patients with CD treated with osilodrostat for 12 weeks, which was followed by open-label osilodrostat administration for 36 weeks; overall, the study lasted for a total of 48 weeks.[9] For the first 12 weeks, osilodrostat was compared to placebo, and then all subjects in the study received osilodrostat until week 48.[9] The study reported that 77% of patients achieved UFC normalization after 12 weeks of treatment with osilodrostat, compared to 8% with placebo, which was statistically significant ($p < 0.0001$).[9,27] As expected, plasma aldosterone levels decreased and the levels of steroid precursors, including 11-deoxycortisol and 11-deoxycorticosterone, increased. In addition to amelioration of hypercortisolism, patients experienced improvements in quality of life as well as beneficial effects on body weight, systolic and diastolic blood pressure, fasting glucose, total cholesterol, and depression clinical scores. Clinical improvements that were achieved within the first 12 weeks remained unchanged until the end of the study. Overall, osilodrostat was well-tolerated. However, 13% of patients had to discontinue the medication due to adverse effects. Adrenal insufficiency was reported in 28% among LINC 4 participants.[20–22,25,27]

After the 48th week, patients who showed benefit from osilodrostat at the end of the study period had the opportunity to enroll in a multicenter, extension phase lasting up to 72 weeks. The average exposure to osilodrostat was 130 weeks. Out of 106 patients who entered the extension phase, 81% achieved UFC normalization by week 72. Improvements in clinical features and quality of life remained stable in comparison with the main study. No new adverse effects were noted. This is the largest study of osilodrostat to date and has provided long-term follow-up data in patients with CD.[28]

Clinical Application (Safety, Dose, Efficacy, Titration, Side Effects)

The initially recommended dose for osilodrostat is 2 mg twice daily, except for Asian populations or patients with milder hypercortisolism, wherein the initial dose is reduced to 1 mg twice daily. The medication is taken orally and is available as 1, 5, and 10 mg tablets. It can be taken with food, including fatty meals. The dose is usually titrated every 2–4 weeks and should not exceed 30 mg twice daily. If a dose is missed, the patient should avoid taking an extra dose and should instead take the next scheduled dose.[8,9,21] A slower dose titration may minimize the occurrence of hypoadrenalism. The maintenance dose should be adjusted for each patient individually with a goal of achieving normal cortisol levels based on UFC levels.[20] Of note, 11-deoxycortisol accumulates in the blood and urine of patients treated with osilodrostat as a result of enzymatic blockade, and cross-reacts in several cortisol immunoassays. Cortisol-specific immunoassays or mass spectrometry-based methods can be used to mitigate this issue.

Overall, osilodrostat has a good safety profile and is a generally well-tolerated medication. However, careful monitoring is needed to avoid hypoadrenalism. Most common side effects are nausea, headache, fatigue, decreased appetite, and arthralgias, which may result from hypoadrenalism or glucocorticoid withdrawal. Patients with a known prolongation of the QT_c interval need close monitoring, as osilodrostat can lead to additional QT_c prolongation. When used at the highest therapeutic dose of 30 mg twice daily, the QT_c interval was prolonged by 5.3 msec.[9] Prolonged QT_c intervals have been observed in 4% of patients but have not resulted in arrhythmia.[21] Several studies in humans have reported QT_c prolongation in patients on osilodrostat. It is particularly advisable to implement close monitoring of QT_c intervals, when using osilodrostat/pasireotide combination in humans, since both drugs can result in QT_c prolongation.[9,18]

Osilodrostat has been administered in combination with ketoconazole in a patient with bilateral adrenocortical hyperplasia. Osilodrostat was added since uptitration of ketoconazole dose was limited by side effects. Overall, combination therapy was well tolerated, and the cortisol level was adequately controlled.[29]

Some studies have shown that osilodrostat reduces cortisol levels and improves blood pressure more rapidly, when compared to metyrapone.[26] Decreased cortisol levels after the initiation of treatment may be associated with clinical signs and symptoms of adrenal insufficiency or glucocorticoid withdrawal symptoms, with a prevalence as high as 51% during the titration phase, decreasing to 6% in the osilodrostat group during the randomized withdrawal phase.[21] Patients should be educated about these symptoms and instructed on proper management. If a patient develops evidence of adrenal insufficiency or withdrawal symptoms, osilodrostat should be held or the dose decreased. In case of any acute stress such as acute illness or surgery, osilodrostat should be temporarily held. If a patient is undergoing urgent (non-elective) surgery, then she or he should receive stress-dose glucocorticoids. On the other hand, if surgery is planned, then she or he should stop taking osilodrostat 1 week prior to surgery.[21] In order to minimize the risk of adrenal insufficiency, especially if there is no rush to control the disease in outpatients, it is recommended to start osilodrostat at a lower dose of 1 or 2 mg twice daily and then slowly titrate over the course of 3 to 4 weeks or even longer.[7]

Female patients may exhibit signs of hyperandrogenism as a consequence of elevated serum testosterone levels, including acne and hirsutism. Less common adverse effects include infections, such as urinary tract infection, influenza, nasopharyngitis, as well as asymptomatic neutropenia.[9,20,22] Owing to an increase in aldosterone and cortisol precursors with mineralocorticoid activity, one should be aware of the potential risks of hypokalemia, edema, and hypertension. It is recommended to check serum electrolytes, including potassium and magnesium (risk of hypokalemia) and white blood cell count (risk of neutropenia) prior to starting osilodrostat, 1 week into the treatment and periodically thereafter.[21]

Even though many patients achieve adequate control of CD by surgery and medical management, including osilodrostat, lifelong monitoring of all patients is essential. Currently, there are no data regarding the possible risk of corticotroph tumor progression in patients being treated with osilodrostat. However, careful monitoring of ACTH levels and pituitary imaging are prudent, similarly to patients who underwent bilateral adrenalectomy.[30]

Interactions

As already mentioned, one of the possible risks of osilodrostat therapy involves QT_c prolongation. Thus, it is recommended to obtain a baseline electrocardiogram (ECG) prior to osilodrostat treatment, 1 week after the onset of therapy and periodically thereafter. Prescribers should avoid osilodrostat co-administration with other medications, which may prolong QT_c, including some antidepressants, antipsychotics, macrolides, and fluoroquinolones.[21]

Osilodrostat has been found to be a weak-to-moderate inhibitor of four human cytochrome P450 enzymes, including CYP1A2, CYP2C19, CYP2D6 and, most importantly, CYP3A4/5, and may increase plasma concentrations of other drugs that are substrates for these enzymes. Often, patients with CD have multiple comorbidities requiring various medical therapies. As a corollary, it is very important to recognize potential drug–drug interactions with osilodrostat and avoid potentially interacting medications or adjust medication doses as appropriate.[31] As osilodrostat is a substrate for CYP3A4, its dose needs to be increased if the drug is co-administered with CYP3A4 inducers, such as carbamazepine, phenytoin, phenobarbital, and rifampin; conversely, osilodrostat dose needs to be reduced if the medication is used together with CYP3A4 inhibitors (such as clarithromycin, itraconazole, indinavir).[21]

Special Populations

Ectopic CS is rare and is caused by extrapituitary secretion of ACTH by a neuroendocrine tumor of the lung or islet cells, or other malignancies such as renal cell, breast, or ovarian cancer. It usually causes severe hypercortisolism and can be life-threatening, so early recognition and treatment are essential. Osilodrostat was used as first-line of monotherapy in a patient with severe ectopic CS requiring intensive care unit (ICU) stay. An initial dose of 20 mg/day was rapidly increased to a daily maximal dose of 60 mg/day in just 5 days, resulting in normalization of cortisol levels within only 6 days. Overall, the drug was well tolerated and the patient experienced clinical improvement.[32]

In a multicenter retrospective French study, a total of 33 patients with ectopic CS were included. For 11 patients, osilodrostat was administered as first-line monotherapy, while the other 22 patients were treated with osilodrostat

as second-line monotherapy or combined therapy. In all patients, UFC significantly decreased ($p<0.01$). In addition, there was improvement in hyperglycemia, hypokalemia, and blood pressure control. Adrenal insufficiency was reported in 8 out of 33 patients.[33]

Osilodrostat can be used in patients with severe hypercortisolism secondary to ectopic CS, wherein it is very important to rapidly control cortisol levels; however, clinical experience is still limited in this setting.[34] Of note, osilodrostat therapy has not been FDA-approved in the US for ectopic CS; the drug is approved specifically for CD. In Europe, regulatory approval of osilodrostat for subgroups of patients with CS has not been specified; osilodrostat therapy in patients with either CD or ectopic CS would be considered "within label" use.

In patients with CS caused by adrenal adenoma, osilodrostat may be potentially used off-label to decrease pre-operative cortisol levels prior to adrenalectomy. As aforementioned, there is a risk of adrenal insufficiency, which can be managed with temporary drug withdrawal and supplemental hydrocortisone.[35]

Studies so far have not been performed in patients older than 70 years. As a corollary, it is unclear whether the safety profile and drug efficacy remain the same in older patients.[25] No information is available on the safety of osilodrostat therapy during pregnancy or lactation. Due to the risk of adrenal insufficiency in infants, it has been advised to avoid nursing until 1 week after the last osilodrostat dose.[36]

Summary/Future Directions

Osilodrostat represents an important advance in the pharmacotherapy of CD. Available data suggest that osilodrostat is effective in controlling hypercortisolism in most treated patients with an acceptable safety profile. Careful monitoring is needed in order to avoid hypoadrenalism and assure safety in treated patients.

However, it should be noted that studies involving head-to-head comparisons between osilodrostat and other medical therapies for CD are not available. In addition, long-term safety and efficacy data are needed. It is unclear whether long-term treatment with osilodrostat affects the size of the pituitary tumor in patients with CD and further studies are needed to examine this issue.[25] So far, there are no society guidelines with recommendations for follow-up pituitary imaging and endocrine testing in order to detect the possibility of pituitary tumor progression in patients with CD on osilodrostat therapy, as may occur in patients who underwent bilateral adrenalectomy (corticotroph tumor progression or Nelson's syndrome). In patients with CD who either underwent bilateral adrenalectomy or are maintained on long-term medical therapy, regular monitoring of plasma ACTH levels and pituitary imaging (MRI) is advisable.[30]

Further studies are also needed in order to elucidate the role and examine the efficacy and safety of osilodrostat used in combination with other therapies in patients with severe CD or ectopic CS.

Abbreviations

ACTH, adrenocorticotrophic hormone (adrenocorticotropin); CD, Cushing's disease; CS, Cushing's syndrome; CYP11B1, 11-beta hydroxylase; CYB11B2, aldosterone synthase; GR, glucocorticoid receptor; LAR, long-acting release; UFC, urinary-free cortisol.

Disclosure

The authors report no conflicts of interest in this work.

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