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Commentary

Osilodrostat for the Treatment of Cushing's Disease: Growing Evidence in the Treatment of Rare Endocrine Diseases

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Surgical resection of pituitary adenomas that autonomously produce adrenocorticotropin (ACTH) is the acknowledged first-line treatment of Cushing's disease (CD). However, surgery may be impossible or may have to be delayed in patients in very bad condition and may not be curative, and 10% to 30% of patients in postoperative remission may experience recurrence of CD. Medical treatments may be used in these situations (1).

Until the advent of the third millennium, medical treatments for CD had never been subjected to the rigors of prospective clinical trials, hampering accurate estimation of their efficacy and side effects. The rarity of the disease was also an obstacle to performing large-scale studies. The year 2012 was remarkable for the publication of the first 2 prospective studies (including 1 large-scale and double-blind study [review in (1)]) involving attractive pharmacological agents from a conceptual perspective: pasireotide, acting at one end of the pathophysiological chain by targeting somatostatinergic receptors of the corticotropic adenoma to decrease ACTH production, and mifepristone, acting at the other end of this chain by blocking access of cortisol to its cognate receptor. However, both drugs have limited effectiveness and are associated with significant side effects, without forgetting the lack of a straightforward method to assess the efficacy of mifepristone.

Therefore, and despite the current lack of published rigorous clinical trials, the steroidogenesis inhibitors metyrapone and ketoconazole have remained since the 1980s as the current mainstays of medical treatment for CD, owing to their rapidity of action, efficacy, and tolerance (1, 2). Osilodrostat is a recently approved steroidogenesis inhibitor, acting, like metyrapone, mainly on the last enzymatic step of cortisol synthesis (CYP11B) although with an increased potency and a longer half-life. The development of osilodrostat is typical of that for new drugs, having followed a study program (LINC) that included 2 Phase 3 studies. Linc 3 was a double-blind, randomized, withdrawal phase study published in 2020 (3). Linc 4, the results of which are presented in this journal (4), is a multicenter trial comprising an initial 12-week, randomized, double-blind, placebo-controlled period, followed by a 36-week, open-label treatment period, conducted in 73 patients with CD. Although there are no direct head-to-head comparison studies with ketoconazole and metyrapone, the results of the Linc 4 study confirm a favorable potency of osilodrostat, with 77% of patients achieving normalization of 24-hour urinary free cortisol (UFC), following a titration procedure at the end of the double-blind phase and using a reduced number of pills taken in 2 daily intakes. Normalization of UFC was rapidly observed (within 5 weeks in 58% of patients) and was obtained in 81% and 69% of treated patients at week 36 and 48, respectively, of the open-label period. As expected, CD comorbidities improved with the reduction of hypercortisolism and were associated with an improvement in perceived quality of life. Predictable, and previously described, side effects (2, 3) were mainly due the accumulation of steroid precursors upstream of the enzymatic blockade, but drug tolerance was acceptable, as reflected by a discontinuation rate due to adverse events of 11% (4). Interestingly, and as was observed in the Linc 3 study, adrenal insufficiency was a prominent side effect. In such a debilitating disease as CD, adrenal insufficiency can be considered a desirable effect, reflecting the potency of osilodrostat. Importantly, the Linc 3 study (3) and independent experience (including ours) (5) have shown that adrenal insufficiency may occur not only during the titration period but also during mid- and long-term treatment. The possibility of increased potency with long-term exposure to osilodrostat deserves further studies. Physicians and educated patients must be aware of the possibility of adrenal insufficiency and follow clinical vigilance associated with regular measurement of 8 am serum cortisol, since UFC lacks sensitivity in diagnosing adrenal insufficiency. From this perspective, it is worth remembering that, as seen with metyrapone, CYP11B blockade increases 11-deoxycortisol, which may cross-react in some (but not all) immunoassays, leading to overestimation of cortisol values. Before starting treatment, physicians must therefore discuss the cortisol assay to be used with biochemists,

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while acknowledging that liquid chromatography-tandem mass spectrometry is the reference method for monitoring cortisol during CYP11B inhibitor treatment.

The endocrine community can therefore welcome the arrival of a new efficient drug, with appropriately documented effects, in the armamentarium to treat this difficult disease. However, at this stage of our knowledge, what evidence are we missing? I will cite only 3 such gaps. First, and as commonly observed in practice with any medical treatment, the Linc studies show that a subset of patients that is difficult to accurately quantify from the publications (since individual UFC values for each patient were not provided across the course of the study) exhibit fluctuations between controlled and increased UFC. We can estimate this subset to be at least 14% and 18% of controlled patients prior to randomization and in the withdrawal period, respectively, in the Linc 3 study (3), and 12% between week 36 and 48 of the Linc 4 study (4). Large spontaneous fluctuations in cortisol production in CD is common. These may be more pronounced in some patients who should be identified before and during any medical treatment, since they require more frequent biochemical monitoring to adapt the drug dosage and/or use of a different therapeutic strategy such as a block-and-replace regimen (2). Second, although 24-hour UFC represents the integrated daily amount of cortisol production, normalization of UFC does not represent ideal control of the disease as it may be associated with a persistently disrupted circadian rhythm of cortisol secretion as reflected by normalization of late-night salivary cortisol (LNSC) in less than half of the patients with controlled UFC (3, 4). An ancillary study of pasireotide-LAR treatment (6) showed that the best clinical improvement is observed when both UFC and LNSC are normalized. These findings question the accuracy of commonly used biochemical markers to reflect tissue exposure to cortisol and the possibility of using long-term medical treatment in patients with a persistent mild hypercortisolism. Alternative treatment strategies should be considered when repeated LNSC levels remain increased. These include attempts to restore the circadian rhythm with a greater dosage in the evening (assuming a relatively short biological half-life of the drug), association of drugs, or the use of a block-and-replace regimen (2). The last of these has the disadvantages of increasing drug dosage, its inherent cost, the increased probability of side effects, and encountering the imperfections of glucocorticoid replacement. Third, the efficacy and osilodrostat regimen to treat other causes of hypercortisolism should be the subject of future studies. These include more severe cases of hypercortisolism than those included in Linc 4 (4), as seen in patients with ectopic ACTH syndrome (7, 8) and, at the opposite end of the spectrum, mild adrenal cortisol excess due to adrenal incidentalomas, a much more frequent situation, strongly associated with increased cardiac and metabolic morbidity, and in which the benefit of surgery remains uncertain.

Disclosure Summary

A.T. has been involved in clinical research studies and received honorarium as consultant/speaker and research grants from Recordati Rare Diseases, Novartis, and HRA Pharma.

Data Availability

Original data generated and analyzed during this study are included in this published article or in the data repositories listed in the references.

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