New Drug Lowers Cortisol in Cushing's Disease Patients

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The European Commission and United States Food and Drug Administration (FDA) have both recently given the green light to market a new drug designed for adult patients with Cushing's disease. This autoimmune disorder, which impacts roughly 13 million people per year, is a form of Cushing's syndrome caused by a benign tumor on the pituitary gland. The tumor causes increased cortisol levels, and the goal of the drug is to lower cortisol levels without the unintended side effects seen with other medications such as hyperglycemia or liver damage.

Osilodrostat, which is being marketed under the brand name Isturisa, is a drug designed for Cushing's disease patients who have been unresponsive to pituitary gland surgery or are unable to get surgery. The medication was originally manufactured by Novartis Pharmaceuticals and eventually sold to Italian pharmaceutical company Recordati Rare Diseases in June 2019.

"We are pleased with FDA's recognition of Isturisa as an effective and safe treatment for patients with Cushing's disease," said CEO Andrea Recordati in a March press release. "Recordati Rare Diseases is committed to working to ensure everyone who needs access to this therapy has it."

The European Commission approved the medication for marketing in the European Union in January 2020, and the FDA approved it for the U.S. in March 2020. However, according to FDA records, osilodrostat was designated as an orphan drug in September 2013, long before it was approved for marketing. This designation means it was approved for the treatment of a condition that affects 200,000 people or less, or that the costs of developing the drug exceed the estimated returns.

The latter is true for Cushing's disease, also referred to as endogenous Cushing's syndrome. Cushing's disease cases comprise 60 to 70 percent of Cushing's syndrome cases in children and over 70 percent of cases in adults, indicating a pre-existing need for the drug.

How does Isturisa work?

Isturisa inhibits 11-beta-hydroxylase, which may also be referred to as steroid 11-beta-monooxygenase. This enzyme converts 11-deoxycortisol to cortisol. Metyrapone also inhibits 11-beta-hydroxylase, but it is primarily used as a diagnostic drug.

According to the National Center for Biotechnology Information, 11-beta-hydroxylase is coded for by the gene CYP11B1, and mutations in this gene can cause congenital adrenal hyperplasia, a condition characterized by excessive

androgen production. The expression of this protein is regulated by adrenocorticotropic hormone (ACTH), the hormone implicated in Cushing's disease.

However, patients with Cushing's disease have excess levels of ACTH due to the presence of the pituitary adenoma. This then increases the concentration of 11-beta-hydroxylase in the body and therefore leads to the hypercortisolism seen in Cushing's disease patients. This gives way to symptoms including bruising, weight gain, excessive hair growth, high blood pressure and rounding of the face.

According to the FDA, an increased dosage of Isturisa leads to an increase in the concentration of 11-deoxycortisol and ACTH. Although ACTH has increased due to low cortisol levels, 11-beta-hydroxylase can no longer convert 11-deoxycortisol, so cortisol levels remain reduced.

Overall, Isturisa reduces cortisol levels by interrupting the biological pathway that leads to cortisol production.

Why is a new drug necessary?

In a 2016 case history published in *The Lancet*, science and medicine historian Richard Barnett states that Cushing's disease has been primarily treated with radiotherapy, cortisone synthesis blockers, and pituitary gland surgery. The latter is usually the first step in treatment according to a 2009 article in the journal *Pituitary*, and the surgery has a 80 percent success rate according to the National Organization of Rare Diseases (NORD). Some reasons a surgery may fail include

incomplete removal of a tumor, comorbid tumors or recurring illness.

If the patient declines surgery or surgery is unsuccessful, radiation therapy may be used to treat the pituitary adenoma. However, author Mary Lee Vance, a professor of medicine at the University of Virginia, writes that remission time is unpredictable and regular monitoring is necessary to determine effectiveness of radiation therapy. Additionally, NORD states that radiation therapy only improves symptoms in 85 percent of patients.

This leaves the third option - cortisone synthesis blockers - which is where Isturisa comes in.

Other medications that have been used to lower cortisol levels include ketoconazole, cabergoline and pasireotide. While all have shown success in lowering cortisol levels, some have limited effects or unintended side effects. For instance, pasireotide has been associated with elevated glucose levels due to reduced insulin and glucagon-like peptide-1 (GLP-1). Cortisol already hinders glucose metabolism and insulin secretion in Cushing's disease patients, and as such treatments are geared towards alleviating impaired metabolism. Therefore, drugs like pasireotide would only reduce the efficacy of such treatments. Similarly, ketaconazole resulted in increased hepatotoxicity after long-term use.

On the other hand, although cabergoline targets the pituitary gland, it only reduced cortisol levels in 20 percent of patients. In contrast, the FDA's decision to approve Isturisa was primarily influenced by a 48-week clinical trial where half of the 137 participants had normal cortisol levels by the 24-week mark, according to BioSpace. Additionally, 86 percent of patients who continued to receive the drug during a randomized withdrawal trial maintained normal cortisol levels.

This medication would be particularly useful in place of previous treatment regimens which combined multiple drugs in order to maintain control over cortisol and other biological compounds.

Future Studies

Isturisa is currently approved for adults only, but as of March 16, 2020, Novartis Pharmaceuticals was recruiting for a pediatric clinical trial. The study would examine the pharmacokinetics and pharmacodynamics of osilodrostat in children, meaning that it would look at how the drug impacts their hormones and other physiological functions.

Future studies could also focus on the effects of Isturisa in patients with other forms of Cushing's syndrome. Another study that examined the effects of osilodrostat in such patients was completed in March 2020. The study began with nine participants but only three completed the trial, with at least four discontinuing due to an adverse event. A larger study with greater retention could yield clearer results in this area.

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