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Signifor® Receives FDA Approval for the Management of Cushing's Disease

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Abstract

Cushing's disease is a disorder characterized by supraphysiologic levels of circulating cortisol due to excessive adrenocorticotropic hormone (ACTH) secretion. Most often hypersecretion of ACTH is due to a pituitary adenoma, where surgical resection of the tumor is considered first-line treatment for the disease. Alternatively, the FDA has recently approved the somatostatin analogue, Signifor® (pasireotide), for the management of Cushing's disease in patients for whom surgery is not an option. In clinical trials, pasireotide has shown a statistically significant reduction in urinary free cortisol levels, as well as significant improvements in quality of life. Based on current data, pasireotide appears to offer a new potential treatment option for patients who are poor candidates for surgery.

Disease State Overview

Cushing's disease, also known as pituitary ACTH dependent Cushing's syndrome, is a rare adrenal disorder characterized by excess glucocorticoid release. While Cushing's syndrome broadly encompasses a number of pathophysiologic causes, the term Cushing's disease is specifically reserved for hypercortisolism resulting from excess ACTH.[1] Most commonly oversecretion of ACTH is due to a pituitary adenoma, causing hypersecretion of cortisol from the adrenal glands. Excessive levels of cortisol can result in weight gain, muscle wasting, hypertension, hirsutism, and a number of other related symptoms.[2]

Each year hypercortisolism is diagnosed in approximately forty out of every million patients. Hypercortisolism generally affects females more than males, and it is most commonly observed in adults during their twenties and thirties while children are nearly unaffected.[1] Cushing's disease often results in chronic hypertension, diabetes, hyperlipidemia, and increased hypercoagulability and is possibly fatal if untreated.[1,2]

The most common symptom noted in Cushing's patients is obesity marked by abnormal fat distribution. Fat is typically deposited centrally, especially in the face and neck (resulting in a characteristic "buffalo-hump"), while the muscles of the arms and legs atrophy. Protein wasting can result in thin skin, stretch marks, slow healing, and osteoporosis. Excess androgen production can cause acne, hirsutism, and menstrual irregularities.[1]

In terms of treatment options, surgery to remove ACTH secreting pituitary tumors should be considered first-line. If the tumor is inaccessible for surgery, clinicians may resort to radiation therapy or adrenal resection in an attempt to suppress cortisol production. Alternatively, mifepristone (Korlym®), indicated in the management of Cushing's-related hyperglycemia due to its ability to antagonize glucocorticoid receptors, may be considered. Non-FDA approved, second-line medications may also be utilized, including ketoconazole, mitotane, or metyrapone, which interfere in adrenal steroid synthesis. However, none of these medications are desirable because they do not address the underlying cause of the disease nor correct the abnormal functioning of the hypothalamic-pituitary axis.[2] Fortunately, pasireotide may offer a new treatment option in patients for whom pituitary surgery is not an option.

Literature Evaluation

Overall, relatively little data has been published regarding the safety and efficacy of pasireotide in humans. This is likely due to a multitude of factors including, but not limited to, the low prevalence of its intended indication—Cushing's disease. In this literature evaluation three key trials regarding pasireotide will be reviewed. The first, and main trial supporting the utilization of pasireotide for Cushing's disease, is a phase three clinical trial concluding that utilizing pasireotide led to a significant reduction in cortisol levels.[3] The next trial reviewed is a phase two clinical trial with a limited number of subjects that witnessed a controllable adverse event profile for pasireotide and concluded that the agent produced a decrease in cortisol levels.[4] The final study reviewed is a very small trial designed to assess the utility of pasireotide when used alone versus in combination with other agents for the treatment of Cushing's disease.[5] As a result of these studies, the conclusion was that pasireotide may play a beneficial role in medication-based therapy for individuals with Cushing's disease. Each of these trials will be analyzed in-depth including study results, strengths, and weaknesses.

The main efficacy trial supporting the use of pasireotide for Cushing's disease is a year-long phase three study conducted by Colao et al.[3] Eligible patients for this trial included adults (>18 years of age) with confirmed persistent or recurrent Cushing's disease (or a new diagnosis if they were not candidates for surgery). Cushing's disease was defined as having a urinary free cortisol level of at least 1.5 times the upper limit of the normal range. The primary endpoint for the study was a normalized urinary free cortisol level without any dose adjustments. Secondary endpoints included normalized urinary free cortisol levels regardless of dose adjustments, changes in clinical signs and symptoms, quality of life and safety.[3]

In the study conducted by Colao et al., 162 patients were randomly assigned to one of two pasireotide dosing groups: 600

μg twice daily or 900 μg twice daily. Power calculations had concluded that 146 enrolled patients would provide 87 percent power given a null hypothesis that less than 15 percent of patients would meet the primary endpoint. Any patient at month 3 who had a urinary free cortisol level less than two times the upper limit of the normal range was maintained on (and kept blinded to) their assigned dose through month 6. All other patients were un-blinded to their treatment group and titrated up to a more efficacious dose at a rate of 300 μg twice daily per change. At month 6, all patients entered an open-label phase lasting through month 12. During this phase, dose increases (up to a maximum dose of 1200 μg twice daily) were provided as necessary to any patient whose urinary free cortisol levels remained above the upper normal limit.[3]

In terms of urinary free cortisol levels, a statistically significant reduction was seen at month 6 in the group that solely received 900 μg twice daily. When patients who had received elevated doses starting at month 3 were included, there was a significant reduction in urinary free cortisol levels for both treatment groups at month 6. It was noticed that patients with lower baseline urinary free cortisol levels responded better to pasireotide. Additionally, the reduction in urinary free cortisol levels typically occurred in the first two months of treatment, which were sustained throughout the remainder of the 12-month trial period. In addition to urinary free cortisol levels, other signs and symptoms were also reduced at month twelve. Systolic blood pressure ($p=0.03$), diastolic blood pressure ($p=0.03$), LDL cholesterol (95 percent confidence interval (CI) -23 to -8 mg/dL), weight ($p<0.001$), and quality of life scores (95 percent CI 6.8 to 15.5) were all significantly improved.[3]

Overall, the most common adverse events (observed in >25 percent of all patients) seen in the study conducted by Colao et al. were diarrhea, nausea, hyperglycemia, cholelithiasis and headache. Most of these issues were relatively minor in severity; however, hyperglycemia (actual values were undefined by the authors) was considered a severe issue in 13 percent of all patients. This finding warrants consistent and steadfast monitoring of blood glucose levels in patients on pasireotide for Cushing's disease.[3]

A precursor to the phase three trial described above was a phase two open-label proof-of-concept trial designed by Boscaro et al. to assess the safety and efficacy of pasireotide in Cushing's disease. The inclusion and exclusion criteria are nearly identical to those described above, and the dosage used in the study was 600 μg twice daily. As is typical with phase two clinical trials, there were very few patients involved ($n=39$) and no power calculations were conducted. The study showed that the average urinary free cortisol level of the patients decreased from baseline by over 40 percent ($p=0.021$) and that 76 percent of all enrolled patients witnessed a decrease in urinary free cortisol levels.[4]

In addition, there was a small trial ($n=17$) conducted by Feelders et al. looking to establish potential synergistic effects of utilizing pasireotide in combination with the dopamine-receptor subtype 2 agonist cabergoline and the steroid enzyme inhibitor ketoconazole.[5] The study dosed pasireotide 100 μg three times daily for 15 days with a primary outcome of normalized urinary free cortisol levels. If levels had not normalized by day 15, the pasireotide dose was increased to 250 μg three times daily. If the levels still had not normalized by day 28, cabergoline was added at a dose of 0.5 mg every other day. If urinary free cortisol levels remained elevated, the add-on cabergoline dose was increased to 1.0 mg every other day at day 33 and 1.5 mg every other day at day 38. Ketoconazole was added at a dose of 200 mg three times daily on day 60 if the urinary free cortisol levels still remained elevated. Pasireotide monotherapy normalized the urinary free cortisol levels of five patients (29 percent), pasireotide-cabergoline combination therapy normalized an additional four patients (24 percent), and pasireotide-cabergoline-ketoconazole combination therapy induced biological remission in a total of 15 of 17 enrolled patients (88 percent) by the 80-day trial endpoint. No safety data was assessed in this trial. These data, while lacking power and repetition, suggest that utilizing pasireotide in combination with other clinically available medications may be a worthwhile therapeutic endeavor in the treatment of Cushing's disease.[5]

These trials showcase the best data available regarding this medication; however, they all possess key limitations that jeopardize the clinical validity of the conclusions. The two main clinical trials by Colao et al. and Boscaro et al. with regard to pasireotide in Cushing's disease were both funded and designed by the manufacturer, Novartis. This fact may introduce bias and should be considered when analyzing the data; however, it may be unavoidable due to the orphan nature of the medication.[3,4] The low prevalence of Cushing's disease also contributed to the low sample size in each of these trials and the ultimate limitations associated with a small sample.

The inclusion criteria for the trials by Colao et al. and Boscaro et al. required cortisol levels to be significantly elevated (at least 1.5 times the upper limit of normal). This restrictive inclusion criteria allows for the potential over-exaggeration of the effects of pasireotide on cortisol levels. Therefore, the clinical significance of the medication may have been overstated due to the study design. Similarly, the primary endpoints in all of these studies was change in urinary free cortisol (UFC) levels. While it is true that UFC levels are indicative of adverse events concerning Cushing's disease, the primary concern in this disease state is the development of the pituitary tumor. Only the phase three trial addressed the effects of pasireotide on tumor size, and it was merely mentioned. Additionally, no formal statistics were done on the data and no conclusions were drawn on the effects of pasireotide on tumor size. This lack of proven efficacy against the primary cause of Cushing's disease may limit the clinical use of the medication.[3,4]

It is critical to state the limitations of the final study by Feelders et al. regarding pasireotide alone versus combination therapy. The study was made up of only 17 patients, making it a little more expansive than a case series. The trial was

entirely open-label, thus allowing for the likely result of confirmation bias. Additionally, few safety data or mechanisms for data collection were presented. Overall, it is quite unclear how the data was attained, and given the open-label nature of the study, this makes the conclusions of the study worthy of skepticism. Even given the drawbacks of this study, the decision to include it in the discussion was due to the fact that it provides some context for how pasireotide might actually be utilized in clinical practice for the treatment of Cushing's. This is viewed as critical information for pharmacists to possess as pasireotide makes its way to the market and into clinical practice.[5]

Pharmacologic Management of Cushing's disease

Secondary to the presence of a corticotropin-secreting pituitary adenoma, the chronic hypercortisolism of Cushing's disease has been treated primarily through transsphenoidal surgery.[6] This procedure involves the removal of pituitary tumors with a microscope or endoscope through the sphenoid sinus. Inconsistent remission rates and lack of clinical efficacy in second-line drug therapies have driven the need for alternative medication therapy options.[6] Pasireotide (Signifor®) is indicated to reduce urinary free cortisol levels in adult patients with Cushing's disease who do not qualify for or have not benefitted from pituitary surgery.[7]

The initial dose recommendation for pasireotide is a 0.6 mg or 0.9 mg subcutaneous injection twice daily, which should be titrated based on patient outcomes within the recommended range of 0.3 to 0.9 mg twice per day. Optimal treatment response is measured through 24 hour urinary free cortisol levels. Patients demonstrating symptomatic improvements should continue therapy as long as it remains beneficial for their disease state. If a dose reduction is indicated due to patient intolerance or adverse reactions, it is recommended to adjust in 0.3 mg intervals.[7] In patients with moderate hepatic impairment (Child Pugh B), the maximum dosage recommendation is 0.6 mg twice per day. Prescriptions for pasireotide require the completion of an enrollment form, and it is available exclusively through a specialty pharmacy.[8] Cost information is not yet available.[7]

Overall, the pasireotide studies conducted to date indicate the following adverse events occur in greater than 20 percent of patients: headache, hyperglycemia and related symptoms, diarrhea, nausea, cholelithiasis and abdominal pain.[9] The elevated frequency of gastrointestinal (GI) symptoms and cholelithiasis in the phase three clinical trial was noted to be comparable to existing somatostatin analog side effects.[6] Therapy modification should be considered for patients prescribed pasireotide concomitantly with cyclosporine or moderate risk QT-prolonging agents. Concomitant therapy should be avoided with high risk QT-prolonging agents, mifepristone, and ivabradine due to the risk of enhancing QT prolongation effects.[9] These and other special considerations which require monitoring through the duration of therapy are further explained below.

Clinical trials have elucidated a number of special considerations that must be taken for every patient receiving pasireotide therapy. Due to the mechanism of ACTH suppression, patients may experience weakness, fatigue, nausea, and other symptoms characteristic of hypocortisolism. Options for treating hypocortisolism include temporarily reducing the dose or discontinuing pasireotide and initiating glucocorticoid replacement therapy.[7] Studies conducted in healthy adult patients have also indicated that hyperglycemia may occur as a result of pasireotide treatment. The drug-induced decrease in insulin and insulin secretion is responsible for this adverse event, as opposed to alterations in insulin sensitivity that may result from the original disease state.[6] Seventy-three percent of phase three study participants experienced adverse events due to hyperglycemia, which in many cases led to the development of pre-diabetes and diabetes.[6] Patients with uncontrolled diabetes mellitus should be stabilized with an anti-diabetic agent prior to initiating pasireotide therapy, and the development of hyperglycemia should also be treated with an anti-diabetic agent.[7] Self-monitoring of blood glucose is imperative during the first few months to both optimize treatment and stabilize blood glucose levels. Additionally, bradycardia and prolongation of the QT interval are further clinical findings. Two percent of patients in the phase three trial experienced a QT prolongation which did not require intervention.[6] Special caution must be taken in patients with existing cardiac disease, hypokalemia, hypomagnesemia, congenital QT prolongation and therapy with other substances that prolong the QT interval. In addition, electrolyte imbalances must be corrected prior to initiation of therapy.[7] Liver enzymes may be elevated during the course of therapy, as evidenced by aspartate aminotransferase (AST) and alanine aminotransferase (ALT) measurements three times greater than the upper limit of normal and elevated bilirubin levels during phase three testing. It is appropriate to monitor enzyme levels after one to two weeks of treatment, monthly for three months, and then every six months. If levels are normal initially and rise to be three to five times greater than the upper limit of normal, values need to be confirmed through repeated laboratory testing. Consistently elevated liver enzymes necessitate the discontinuation of pasireotide therapy until levels are resolved and causes are determined. Due to the number of considerations that need to be taken with regard to pasireotide, it is important for patients to have a baseline fasting glucose level, hemoglobin A1C test, liver tests and an electrocardiogram (ECG) in order to respond appropriately to concerns and optimize therapy.[7]

Pharmacists should educate patients on proper administration. Pasireotide, a clear and colorless solution, is manufactured and distributed by Novartis as 0.3 mg/mL, 0.6 mg/mL, and 0.9 mg/mL single dose ampules. It is administered as a 45° angle subcutaneous injection into a fatty area of healthy skin in the upper thigh or abdomen. Rotation of injection sites is an important counseling point to prevent the buildup of scar tissue and ensure proper drug absorption. Patients should be provided a sterile syringe, a long sterile needle (if instructed by physician to draw up medication from the ampule), and a short sterile needle for self-administration. Ampules should be stored at room temperature, protected from light, and discarded if discoloration or particulate mat-

ter is present.[8] If wheezing, chest tightness or other symptoms of a serious allergic reaction occur, patients should contact their doctor.[9] To assist with compliance, an FDA approved medication guide must accompany pasireotide upon dispensing.[8]

Conclusion

Cushing's disease represents a state of excess cortisol secretion, and is commonly manifested by central obesity, protein wasting and hypertension. While pituitary resection is considered the treatment of choice, lack of efficacy among second-line pharmacologic treatments has prompted a need for alternative medications. Fortunately, twice daily pasireotide appears to offer hope for patients who are not candidates for surgery or for those who have previously failed surgical treatment. In clinical trials use of pasireotide resulted in significant reductions in urinary free cortisol levels, as well as improvements in quality of life and secondary symptoms.[3] In terms of side effects, pharmacists should inform their patients that pasireotide may cause headache, hyperglycemia, nausea, diarrhea and may increase the risk of developing gallstones.[9] Overall, however, pasireotide is generally well-tolerated and appears to offer a new, innovative approach toward managing Cushing's disease.

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