



Editorial

## Pituitary-Directed Drug Therapy for the Treatment of Cushing's Disease

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Cushing's disease (CD) is usually the result of an adrenocorticotrophic hormone (ACTH)-secreting pituitary adenoma. The result is overstimulation of the adrenal glands leading to chronic hypercortisolism [1]. Individuals with CD have increased risks of hypertension, obesity, hyperglycemia, infections, and vascular damage. Transsphenoidal surgery of the pituitary adenoma is the preferred option in the treatment of CD. The success rates are 65-90% for microadenomas; however, as many as 40% of patients will experience recurrence within 10 years. A second surgery is an option in only select cases. Radiotherapy is an alternative in some patients, but requires a prolonged time to control the disease and may also lead to hypopituitarism. Bilateral adrenalectomy offers an optional surgical choice, but may be associated with Nelson's syndrome in as high as 30% of patients. Furthermore, glucocorticoid and mineralocorticoid replacement is required throughout the patient's life. Thus, therapeutic management of CD is of primary importance [2].

Adrenal-directed drug therapy has been utilized to decrease cortisol levels. These drugs include ketoconazole, aminoglutethimide, metyrapone, mitotane, and etomidate, and they exert their effect by inhibition of steroidogenic enzymes such as 11 $\beta$ -hydroxylase and 17 $\alpha$ -hydroxylase. Unfortunately, these compounds have limited efficacy and produce significant side effects. Furthermore, they do not target the source of the ACTH-secreting pituitary tumor [3]. Mifepristone is approved for control of hyperglycemia that is associated with Cushing's syndrome. Although elevated levels of cortisol remain, the glucocorticoid receptor is blocked by the antagonist action of mifepristone. Since mifepristone has 10-fold higher binding affinity than cortisol at the glucocorticoid receptor, the adverse effects due to cortisol are blocked by the antagonist [3,4]. Currently, three types of agents are either under clinical investigation or approved that are pituitary-directed therapies. These include the peroxisome proliferator-activated gamma (PPAR $\gamma$ ) agonists rosiglitazone and pioglitazone, the dopamine D<sub>2</sub> agonist cabergoline, and the somatostatin peptidomimetic pasireotide. PPAR $\gamma$  agonists such as rosiglitazone and pioglitazone have demonstrated antiproliferative and apoptotic effects. Clinical studies with rosiglitazone and pioglitazone have involved a small number of patients and little change in cortisol levels has been observed. Furthermore, the increased risks of cardiovascular side effects make PPAR $\gamma$  agonists less than ideal

in the treatment of CD [4]. Since dopamine D<sub>2</sub> receptors are found in approximately 80% of corticotroph adenomas, the D<sub>2</sub> receptor agonist cabergoline has been evaluated in small clinical studies involving CD patients. In a study with 20 patients, cabergoline caused a sustained reduction in cortisol levels in 40% of patients after two years of treatment [5]. Another study with 30 CD patients showed that cabergoline produced a complete response in 9 patients after a mean long-term treatment of 37 months [6]. Nevertheless, additional studies in a larger patient population are needed to confirm these results. Somatostatin (somatotropin release-inhibiting factor, SRIF) is a cyclic tetradecapeptide that occurs in two biologically active forms, SRIF-14 and a N-terminally extended form SRIF-28. SRIF exerts a variety of inhibitory actions including inhibition of insulin and glucagon release from the pancreas and growth hormone release from the pituitary. SRIF also exhibits antiproliferative actions, and it acts as a neurotransmitter or neuromodulator. SRIF exhibits its diverse pharmacological actions by binding to a family of structurally-related G-protein-coupled receptors designated sst<sub>1</sub>-sst<sub>5</sub>, SRIF-14 and SRIF-28 bind with high affinities to all five SRIF receptor subtypes; however, the therapeutic effectiveness of the natural SRIF forms is limited by rapid proteolytic degradation. Thus, the development of more metabolically stable analogues is of intense interest [7-9]. Structure activity studies of SRIF-14 have shown that Trp8 and Lys9 comprise the critical  $\beta$ -turn and that Lys4, Phe6, Phe7, and Phe11 are important for binding to the five SRIF receptor subtypes. Utilizing the essential structural features of SRIF-14, a stable cyclohexapeptide with high affinity (0.1-10 nM) at sst<sub>1</sub>, sst<sub>2</sub>, sst<sub>3</sub>, and sst<sub>5</sub> was discovered [10]. Formerly designated SOM230, this cyclic hexapeptide (cyclo[(4R)-4-(2-aminoethylcarbamoyl)-L-prolyl-L-phenylglycyl-D-tryptophyl-L-lysyl-4-O-benzyl-L-tyrosyl-L-phenylalanyl-]) was approved by the European Commission on April 25, 2012 [11] and by the FDA on December 14, 2012 [12] as pasireotide diaspartate (Signifor<sup>TM</sup>, Novartis) for the treatment of CD in patients who require therapeutic intervention. Due to its relatively long half-life of 12 hours, pasireotide is administered twice daily to maintain steady-state levels. Although pasireotide binds to four of the five SRIF receptor subtypes, activation of sst<sub>5</sub> is thought to be especially significant in inhibiting ACTH release in ACTH-secreting pituitary adenomas. In a phase III study involving 162 patients treated with either 600  $\mu$ g or 900  $\mu$ g two times a day, pasireotide was shown to significantly reduce cortisol levels in CD patients. Additionally, tumor volume was decreased by 43% with the larger dosage. In this study, hyperglycemia was reported in 40% of the patients. Other adverse effects were diarrhea (58%), nausea (52%), and gallstones (30%) [13]. Although no studies are currently underway, it was suggested that mifepristone could be of potential benefit to offset hyperglycemia caused by pasireotide [3]. Since pituitary-ACTH secreting adenomas express D<sub>2</sub> receptors in addition to SRIF receptor subtypes, combination of the D<sub>2</sub> agonist cabergoline with pasireotide was studied in 17 patients over 80 days using urinary free cortisol as the endpoint. Approximately, 50% of patients had reduced urinary cortisol after two months [14]. The addition of ketoconazole led to a complete response in 15 out of 17 patients; however, larger studies are required to determine if this combination therapy is viable.

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Cushing's disease is a devastating disease with increased morbidity and mortality. Although transsphenoidal surgery is the preferred first choice of treatment, many CD patients are not controlled by this procedure. As a result, pituitary-directed therapies offer a significant alternative for those individuals. The recent approval of pasireotide offers another option for those individuals in which surgery is not possible or has failed. Although hyperglycemia is a major adverse effect with pasireotide, it seems possible to treat this with antidiabetic drugs. Additional studies are needed to determine the effectiveness of combination therapies such as cabergoline and pasireotide. In conclusion, new drug therapy as exemplified by pasireotide offers new hope for combating CD.

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