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CASE REPORT

Effectiveness of low-dose pasireotide in a patient with Cushing's disease: antiproliferative effect and predictivity of a short pasireotide suppression test

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Key Clinical Message

This case shows efficacy of low-dose pasireotide in biochemical and clinical control of severe hypercortisolism and in tumor volume reduction in a patient with an ACTH-secreting macroadenoma. The drug may be an option for long-term treatment in some patients where control of tumor mass is an important clinical endpoint.

Keywords

ACTH-secreting macroadenoma, antiproliferative effect, Cushing's disease, pasireotide.

Introduction

First-line treatment of Cushing's disease (CD) is pituitary microsurgery; medical treatment has been limited to patients with persistent hypercortisolism after unsuccessful surgery, while awaiting the beneficial effects of radiation therapy or, preoperatively, to control symptoms due to extremely severe hypercortisolism in order to reduce the surgical risk [1]. Drugs so far available target adrenal cortisol production via steroidogenesis inhibition (ketoconazole, metyrapone, etomidate) or act by blocking glucocorticoid action at the glucocorticoid receptor (mifepristone) or combine antisteroidogenic and adrenolitic action (mitotane) [2, 3] Until short time ago, only cabergoline was an available pituitary targeted therapy [4].

Overall, there is no substantial evidence in support of many of the drugs currently used in treatment of hypercortisolism; many are used off-label, are unavailable in some countries and no reliable predictors of efficacy are identified.

Pasireotide is a novel somatostatin analog that acts on specific receptor isoforms with increased affinity toward sstr 5 in comparison with previous analogs [5]. In this case report, we show that low doses of pasireotide used as first-line treatment in a patient with CD not eligible for surgery were effective in normalizing cortisol secretion and improving the clinical condition and also in determining substantial tumor volume reduction.

Case Description

A 63-years-old male patient was referred to emergency room after 2 days of acute onset headache, diplopia, visual impairment, nausea, and vomiting; when admitted to the Hospital only diplopia persisted. The past medical history was unremarkable except for depression since 20 years. At brain CT and CT-angiography performed in the emergency department a pituitary mass was detected; at subsequent gadolinium-enhanced MRI, a pituitary macroadenoma with suprasellar and right parasellar extension dislocating right internal carotid was detected (21 mm × 14.5 mm × 15.7 mm, respectively, postero-anterior, cranio-caudal, and latero-lateral diameters, volume 2.53 cm^3), isointense with brain on T1 and hyperintense on T2 weighted images, compressing the normal gland and deviating to the left the pituitary stalk (Fig. 1).

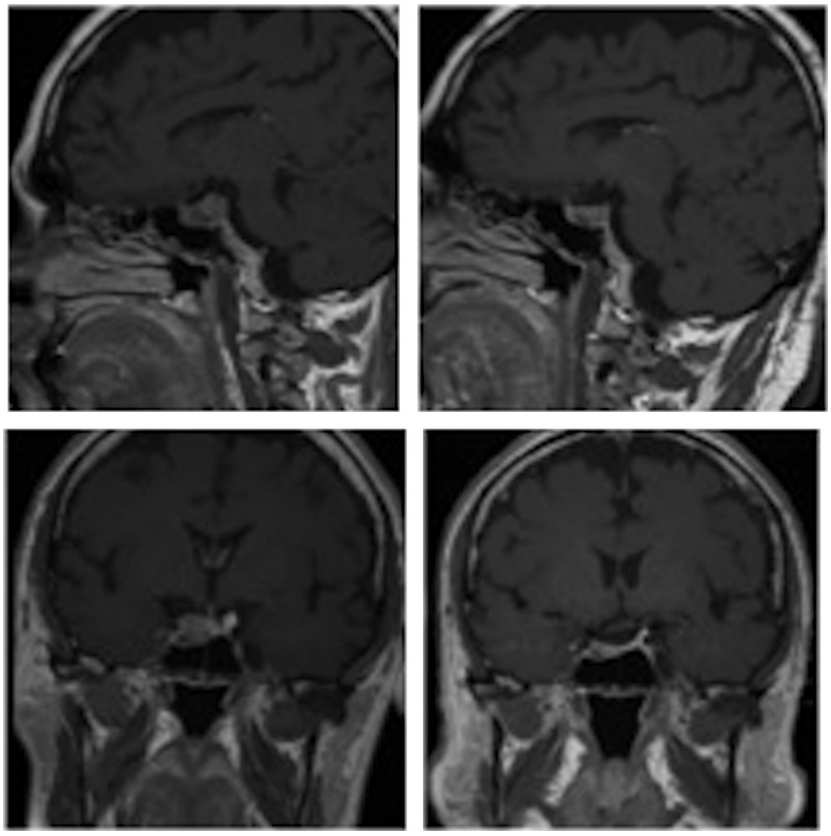

Figure 1. Gadolinium enhanced MRI studies performed at baseline (left) and after 12 months (right) of treatment with pasireotide 300 μg subcutaneously (s.c.) two times a day (b.i.d).

Opthalmological evaluation was normal. Full-blown cushingoid features were present with newly diagnosed hypertension and impaired glucose regulation (HbA1c 44 mmol/mol) treated, respectively, with hypotensive drug and diet. Densitometric values were consistent with osteopenia.

High-normal plasma ACTH levels (88 and 43.2 pg/mL, n.v. 9–52), elevated 24 h urinary free cortisol excretion (UFC) (459 μg/24 h, normal range 36–137) were detected as well as normal thyroid function and normogonadotropic hypogonadism. Hypercortisolism was confirmed by repeated UFC collections (UFC 2601, 1075, 6222 μg/24 h), unsuppressibility of cortisol after low-dose dexamethasone (320 μg/L) and by supranormal midnight plasma cortisol (172 μg/L, n.v. <75 μg/L) (Table 1). Plasma ACTH increased by 35% after desmopressin and by 18% after CRH (basal 60 and peak 71 pg/mL at 60 min), whereas plasma cortisol was not responsive (basal 393 and peak 405 μg/L at 15 min); plasma and urinary cortisol decreased by 75.3% and 66.3% after high-dose dexamethasone suppression test.

Clinical signs and symptoms of overt Cushing's syndrome were worsening since the first evaluation 2 months before: blood pressure levels had increased, cholesterol levels were higher than before, glycemic control worsened and Hba1c value consistent with overt diabetes was found (HbA1c 49 mmol/mol) (Table 1). Metformin was therefore started.

Pituitary surgery was recommended: as the patient refused surgery, primary medical treatment with subcutaneous pasireotide (SOM230; Novartis, Basel, Switzerland) was offered at the initial dose of 0.6 μg, bid.

Short Pasireotide Suppression Test

ACTH and cortisol variations after 100 μg octreotide were compared with those recorded after the first dose of pasireotide. Octreotide did not induce changes, whereas a progressive decline in cortisol concentration was recorded with maximal inhibition of 67% at 10 h after administration of pasireotide (Table 2, Fig. 2).

Two weeks later, plasma ACTH normalized (47 pg/mL) and UFC decreased (564 μg/24 h) (Fig. 3). A worsening of glycemic control required an increase of metformin dose and addition of sitagliptin.

Table 1. Biochemical and hormonal data at baseline and during treatment with pasireotide.

	UFC[1] (μg/24 h)	ACTH (pg/mL)	HbA1c (mmol/mol)	Total cholesterol (mg/dL)	Tryglicerides (mg/dL)	HDL (mg/dL)	Weight (kg)	BMI	WAIST (cm)
Basal	3299	65	49	237	112	53	88	29.4	105
2 weeks	564	47							
Month 1	27	31	76				86	28.7	102
Month 2	46	21	77						
Month 3	522	52	53				84.4	28.2	
Month 4	30	17	53						
Month 6	54	15	55	210	129	42	82.5	27.5	101
Month 9	55	17	50				82	27.4	98
Month 12	38	16	49	188	106	40	80	26.7	97
Month 14	218	51	45						
Month 15	38	40					80	26.7	96
Month 18	82	30	47	167	95	38	78	26	96

[1]Mean of four values.

Table 2. Left: Plasma ACTH and cortisol levels before and hourly for 6 h after a single dose of 100 μg s.c. octreotide. Right: Plasma ACTH and cortisol levels before and every 2 h for 10 h after a single dose of 600 μg s.c. pasireotide.

	Short pasireotide suppression test	
	Serum cortisol (μg/L)	ACTH (pg/mL)
Basal	315	110
2	150	32
4	119	38
6	143	45
8	106	40
10	100	35.6

One month later, the patient complained of fatigue, dizziness, abdominal pain, and diarrhea, consistent with hypoadrenalism; UFC had decreased to subnormal values (27 μg/24 h). Hypotensive drugs were reduced; due to unsatisfactory glycemic control insulin treatment was started.

On the basis of clinical and biochemical data, pasireotide was reduced to 0.3 μg twice daily.

Starting from the third month of treatment, the improvement of the clinical condition persisted steadily for 18 months (at the present time) in line with normalization of UFC concentrations (Fig. 3). Testosterone concentration normalized. Fasting, postprandial glucose, and Hba1c values were satisfactory on long-acting insulin, metformin, and sitaglyptin (fasting glycemia values <130 mg/dL and postprandial values <180 mg/dL); cholesterol profile improved. Blood pressure normalized without treatment, weight decreased by more than 10% and waist circumference from 105 to 96 cm. Antidepressant therapy was also stopped.

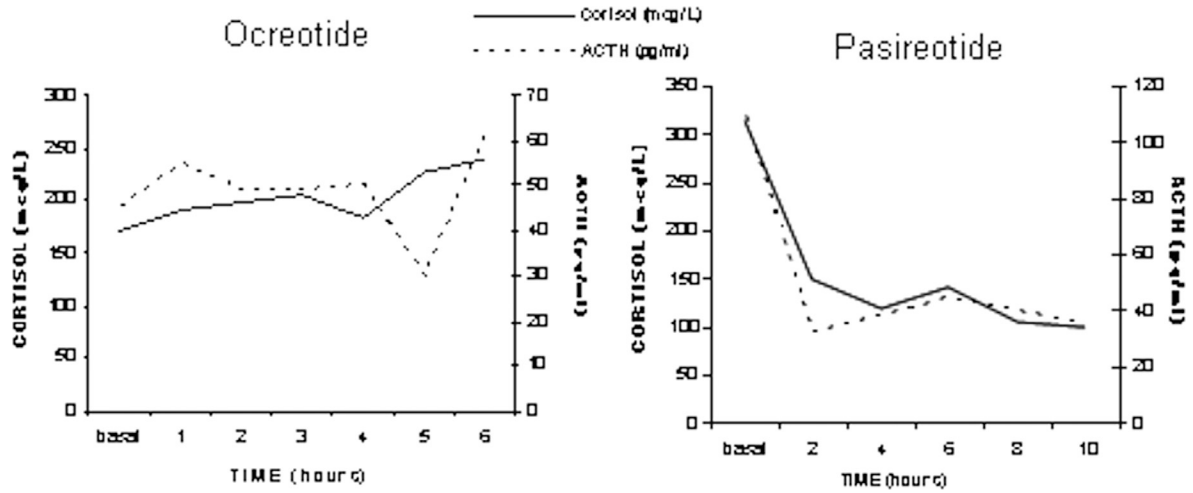

Figure 2. Left: Plasma ACTH and cortisol levels before and hourly for 6 h after a single dose of 100 μg subcutaneous octreotide Right: Plasma ACTH and cortisol levels before and every 2 h for 10 h after a single dose of 600 μg subcutaneous pasireotide.

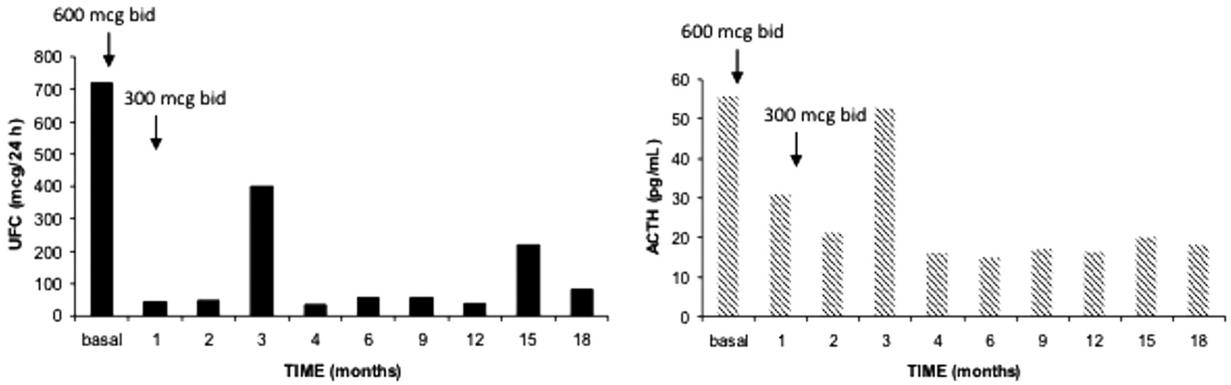

Figure 3. Urinary-free cortisol (UFC) excretion (normal range: 37–136 μg/24 h) and plasma ACTH (normal range 9–52 pg/mL) values before and during the entire course of pasireotide treatment.

Overall the patient reported an improvement in quality of life. Although no specific quality of life measure was utilized, the patient reported improvements in the areas of self confidence, physical appearance, social activities, sleep quality, physical performances, and everyday activities.

At MRI, the size of the pituitary tumor decreased by 44% at 6 months and up to 52% at 18 months (18.9 mm × 9.8 mm × 11 mm, volume 1.21 cm^3) (Fig. 1). The BMD values were stable with respect to first evaluation.

Discussion

From a clinical standpoint, a remarkable finding of this case is the effectiveness of low doses of pasireotide in obtaining a stable control of disease in a patient with clinical and biochemical features of severe hypercortisolism, a finding rarely reported previously in single patients [6, 7].

As reported in the registrative trial [8], normalization of UFC was more likely achieved in patients with mild disease, although the drug was effective also in severe hypercortisolism. If confirmed in other cases, the effectiveness of pasireotide at doses lower than previously suggested has practical implications such as the reduced risk of adverse events and the potential reduction of the costs for managing the disease.

No gastrointestinal symptoms appeared. Diabetes worsened during treatment, however, surrogate markers of cardiovascular risk improved as a consequence of the remission of hypercortisolism.

Treatment induced hypocortisolism is an adverse event to be considered in any patient on medical treatment for hypercortisolism: alerting the patient on warning symptoms might help in avoiding severe adverse consequences.

The tumor volume reduction here observed is concordant with the antiproliferative effect already seen in primary cell cultures of human corticotroph adenomas [9, 10]. The molecular mechanism of suppression of cell growth and the role of specific sstrs in transducing growth inhibitory signals in corticotroph tumors need further study.

Data in patients with a measurable tumor support the antiproliferative effect of pasireotide at high doses (900–1200 μg, bid) [8, 11]; the present case shows that even a lower dose of pasireotide retains an antiproliferative effect.

Conclusion

This case illustrates the long-term effectiveness of low doses of pasireotide, a tumor-directed therapy, in the biochemical and clinical control of hypercortisolism of CD. Although it is clear that the control of tumoral mass is best achieved with surgery, the surgical outcome in ACTH-secreting macroadenomas is less favorable than in micro. The drug may be an option for long-term treatment in some patients with the disease when surgery is not feasible for many reasons. It might be an option in patients with ACTH-dependent macroadenomas where control of tumor mass is an important clinical endpoint. The treatment might offer better chance of success for subsequent surgery.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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