Loss of efficacy of pasireotide after its re-administration: is there a reason why?

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Abstract

Pasireotide is a recently approved medical treatment for persistent or recurrent Cushing's disease (CD). However, an escape from the initial successful response has not yet been described. A 42-year-old female presented with several symptoms indicative of hypercortisolism. Biochemical evaluation and imaging were consistent with CD due to a pituitary adenoma. Surgical excision of the adenoma was unsuccessful and gamma-knife radiosurgery was followed. Our patient remained hypercortisolemic thus treatment with pasireotide (900 μg subcutaneously twice daily) was decided. Biochemical and clinical remission was noted shortly thereafter. Moderate adverse events led to dose reduction to 600 μg subcutaneously twice daily. The patient remained in remission for 6 months, when treatment was discontinued due to cholecystitis. One month after cholecystectomy, pasireotide was restarted with no clinical or biochemical benefit that time. Pasireotide is an effective medical treatment for CD. Nevertheless, a loss of its initial efficacy may rarely be described.

Introduction

Cushing's disease (CD) is characterized by excessive secretion of adrenocorticotrophic hormone (ACTH) by a corticotroph pituitary adenoma, which then leads to increased production and release of cortisol from the adrenal glands. Hypercortisolism is responsible for the clinical features of the disease, that most commonly include weight gain with characteristic fat distribution, proximal muscle weakness, hirsutism, purplish skin striae, reduced libido, impaired glucose metabolism, hypertension and psychiatric disorders.[1] More importantly, CD is associated with elevated risk of cardiovascular disease and infections leading to increased morbidity and mortality.[2] Transsphenoidal surgical selective removal of the adenoma remains the current gold standard treatment, leading to remission in 70 to 90% of the cases. However, recurrence rates as high as 10 to 45% are reported, leading to persistent disease.[3] Second-line interventions include reoperation, radiotherapy, bilateral adrenalectomy and drug therapy.

Corticotroph pituitary adenomas express multiple somatostatin receptor (SSTR) subtypes, predominantly subtype 5 (SSTR5).[4] Pasireotide (SOM230) is a novel somatostatin analog (SSA) which binds with high affinity to SSTR5 but also to SSTR2, 3 and 1. In comparison to other SSA (octreotide-lanreotide), pasireotide has a 40-fold higher binding affinity for SSTR5, resulting in effective inhibition of ACTH release and cell proliferation.[5] Administration of pasireotide was found to lead to a significant reduction of urinary free cortisol (UFC) levels in 50 out of 103 patients at 6 months and to improvement of clinical symptoms, such as body weight and hypertension, while the rest developed resistance to its efficacy.[6] This resistance has better been described with the administration of octreotide and lanreotide in acromegalic patients.[7,8] Nevertheless, the loss of efficacy after re-administration of pasireotide may constitute a different problem and few data are reported only regarding the use of octreotide in neuroendocrine tumors.[9] Herein, we report a patient with CD, who received pasireotide after a failed attempt of surgical removal of an ACTH secreting pituitary adenoma. Despite the initial biochemical and clinical remission of the disease with pasireotide, the patient experienced an escape from its efficacy after six months from the initiation of treatment.

Case Report

Patient's history

A 42-year-old female patient was referred to our department for further evaluation due to unexplained progressive weight gain (20 kg over the last 3 years) with fat mainly accumulated in the face, neck and abdomen. The patient reported muscle weakness, decreased libido, oligomenorrhea, depression, anxiety, fatigue (even in small effort), sleep disorders (insomnia), decreased concentration and impaired memory. Her medical history included postsurgical hypothyroidism on thyroxin replacement therapy for the last 10 years; mild hypertension, well-controlled with a β-adrenergic blocker and type 2 diabetes under treatment with metformin. No exogenous use of glucocorticoids was reported.

Clinical and laboratory examinations

At presentation, clinical examination revealed thin skin-easily bruised, purplish abdominal striae and abnormal fat distribution, with a dorsocervical fat pad (buffalo hump), facial fullness (moon face), central obesity (waist circumference = 125 cm, hip circumference = 120 cm, BMI = 35kg/m^2) and thin legs. Severe proximal muscle weakness was noted (patient was unable to lift from a chair) as well as hirsutism on the forearms, face and abdomen (Ferriman-Gallwey score = 18). No acne was observed. Blood pressure was 150/90 mmHg with a normal heart rate.

As signs and symptoms were consistent with hypercortisolism, laboratory evaluation for cortisol excess was decided. A 1-mg overnight dexamethasone (DMZ) suppression test, low-dose DMZ suppression test (0.5 mg of DMZ orally every six hours for two days) and analysis of a 24-hour urine collection for UFC excretion were initially performed. The suspicion of hypercortisolism was confirmed (Tables 1 and 2). Morning plasma ACTH levels were high-normal (47 pg/mL, normal range 10-60 pg/mL). Subsequently, a high-dose DMZ (8 mg) suppression test and a stimulation test with Corticotropin-Releasing Hormone (CRH) were performed and the results were consistent with ACTH-dependent Cushing's syndrome (Table 2). Magnetic resonance imaging (MRI) scan of the pituitary gland was scheduled to detect the potential presence of a pituitary tumor, which revealed a 6mm pituitary adenoma.

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Treatment and follow-up

Transsphenoidal removal of the tumor was scheduled. However, surgical excision of the adenoma was unsuccessful, as carotid artery bleeding ensued. A second attempt for surgical resection of the adenoma was considered unsafe and the patient was referred for gamma-knife radiosurgery. Six months following radiosurgery, biochemical and clinical signs of hypercortisolism were still present.

Medical treatment was decided, in order to avoid the harmful effects of hypercortisolism. The patient was placed on pasireotide 900 μg subcutaneously twice daily. Moreover, repaglinide was added to metformin in order to effectively control her blood glucose levels. The patient's weight and waist circumference, arterial pressure measurement, electrolytes and glucose levels, UFC as well as a CD-specific health-related quality of life (HRQoL) questionnaire were used to assess response to treatment.[10] All data were reported at baseline (before treatment) as well as at 15, 30, 90, 180 days thereafter. A baseline abdominal ultrasound was performed revealing the presence of biliary sludge. Since the patient was not symptomatic, cholecystectomy was not recommended at that time.

Response to pasireotide

Early in the course of treatment (within 2 weeks), progressive weight loss (5 kg) was noted, along with improved concentration and mood. UFC levels normalized (UFC = 171 μg/24h, reference range 55.5-286 μg/24h). Antihypertensive dosage was reduced, as decreases in blood pressure were noted. Blood glucose monitoring revealed an improved control of diabetes. Minor adverse effects were reported, including moderate diarrhea, nausea and vomiting. Diarrhea and vomiting were partially controlled with loperamide and metoclopramide respectively. Consequently, pasireotide dose was reduced (from 900 μg to 600μg subcutaneously, twice daily), still effectively controlling the disease.

At three months, body weight loss (13 kg) (Figure 1), decreased waist circumference (by 10 cm) and improved mood were noted. Response to therapy was associated with an impressive improvement in the patient's HRQoL mainly regarding the patients mental, motor, social and sexual activities. UFC levels remained within the normal range. At six months, clinical features of the disease showed further improvement: weight loss of 17 kg (Figure 1), decreased waist circumference (by 10 cm) and remission of easy bruising was noted. UFC levels were slightly above the normal range.

After 6 months of treatment, the patient presented at the emergency department complaining of pain in the right hypochondrium. At clinical examination, a positive Murphy's sign was present. Body temperature was normal. Biochemical evaluation revealed increased cholestatic enzymes: alanine aminotransferase (ALP) equal to 406 mg/dL (reference range 33-122 mg/dL) and increased γ-glutamyltransferase (γ-GT) equal to 1070 mg/dL (reference range 0-61 mg/dL). Ultrasonography of the liver and biliary tract detected the presence of small stones in the gallbladder. The initiation of ursodeoxycholic acid was decided at a dose of 750 mg. Pasireotide treatment was discontinued and, after a month, laparoscopic cholecystectomy was scheduled.

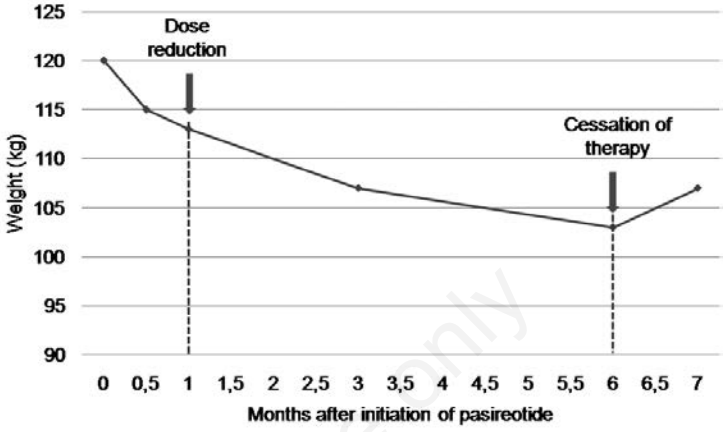

Figure 1. Patient's body weight at baseline and during treatment with pasireotide.

Table 1. Patient's biochemical laboratory examinations at first evaluation.

Biochemical exams	Patient's value	Reference range
Potassium (mmol/L)	4.77	3.5-5.1
Sodium (mmol/L)	140	136-145
Serum glucose (mg/dL)	131	70-105
24-hour UFC (μg/24h)	1st sample: 554 2nd sample: 610.5	36-137
Morning cortisol (μg/dL) (random sample)	25	6.2-19.4
Midnight cortisol (μg/dL)	20	2.3-11.9
Morning cortisol after 1-mg DMZ (μg/dL)	11	<1.8
Morning ACTH (pg/mL) (random sample)	47	1-60

UFC: Urinary Free Cortisol, DMZ: Dexamethasone, ACTH: Adrenocorticotropic Hormone

Table 2. Dexamethasone suppressive and corticotropin-releasing hormone stimulation tests performed to confirm ACTH-dependent disease.

Diagnostic tests	Patient's values	Normal value
Low-dose DMZ suppression test (0.5 mg × 4 for 2 days) (μg/dL)	Morning cortisol after suppression: 7.66	<1.8 μg/dL
CRH stimulation test (pg/mL)	ACTH -15′: 34.5 ACTH 0′: 33.9 ACTH 15′: 63.67 ACTH 30′: 69.23 ACTH 60′: 45.4	
High-dose DMZ suppression test (8 mg DMZ) (μg/dL)	Basal morning cortisol: 25 Next morning cortisol: 6.3	<1.8 μg/dL

CRH, Corticotropin-Releasing Hormone; DMZ, Dexamethasone".

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Loss of efficacy of pasireotide after its re-administration

One month later, levels of ALP and γ-GT returned to normal, but clinical and biochemical relapse of the disease was determined. Body weight had increased by 4 kg and the waist circumference by 2cm since the measurements at the time of treated cessation. For this reason, it was decided to resume treatment with pasireotide 600 μg twice daily (not 900 μg due to prior adverse events with the above dose). Two months after the resumption of pasireotide, despite the previous therapeutic benefit, the patient remained in clinical and biochemical relapse of the disease. Body weight and waist circumference remained stable, while a gradual deterioration of HRQoL was noted. UFC remained steadily elevated.

Discussion

The case reported herein confirms the already proven efficacy of pasireotide in the treatment of persistent CD.[6] Response to treatment was rapid. The patient experienced normalization of UFC within the first 15 days of treatment as well as objective improvement in clinical features of the disease (body weight, arterial pressure, HRQoL). After pasireotide treatment discontinuation, a relapse of the disease was noted but the re-administration of pasireotide was proved ineffective to control the disease.

The clinical efficacy of pasireotide has been demonstrated in a multicenter phase II study,[11] as well as in a large phase III study.[6] In the former, 22 out of the 29 participants (76%) showed a decrease in UFC levels, while five of them (17%) presented normal UFC levels 15 days after the initiation of treatment.[11] The multicenter, prospective, randomized, double-blind phase III study compared treatment with subcutaneous pasireotide 600 or 900 μg twice daily in 162 patients with newly diagnosed or persistent/recurrent CD.[6] This study demonstrated that pasireotide at both evaluated doses, significantly reduces the elevated cortisol levels with a safety profile similar to that of other SSAs (mostly transient gastrointestinal discomfort).[6] One exception is the higher frequency of hyperglycemia occurrence during pasireotide treatment, likely due to inhibition in the secretion of insulin and incretin hormones (glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide). Consistent with this adverse event, the blood glucose profile of our patient was deteriorated and her medical treatment was modified. Based on the above study, pasireotide was approved on April 2012 by M (European Medical Association) for the treatment of refractory or relapsing after surgical treatment CD.[6] Since the patient experienced a life-threatening complication during the surgical procedure, radiotherapy (gamma-knife) was selected as a second-line treatment. In addition, as the patient was experiencing continuous disease progression, the administration of pasireotide (SOM230) was decided, which was given free of charge by the Novartis AG in the context of the compassionate use program for CD. The fact that the patient experienced laboratory remission of the disease two weeks after the initiation of pasireotide is a strong proof of drug efficacy. In addition, the patient relapsed after discontinuation of treatment, which further supports the view that the remission of the disease was due to the administration of pasireotide and not to radiotherapy.

Nevertheless, many patients may present complete or partial resistance to the efficacy of somatostatin analogs due to a variety of clinical, histological and/or molecular factors,[7] as age at diagnosis, tumor size and characteristics on MRI, histology of the pituitary adenoma or genes mutations and polymorphisms.[8] This resistance in pituitary adenoma therapy is better established regarding the administration of octreotide and/or lanreotide, not pasireotide.[8] Recently, ubiquitin-specific protease 8 (USP8) gene mutations are identified in corticotroph pituitary adenomas leading to augmented and more sustained epidermal growth factor receptor (EGFR) signaling. These somatic mutations increase the expression of proopiomelanocortin (POMC) mRNA and the ACTH production by the tumor.[12] It has been proposed that the presence of USP8 mutations predict favorable response to pasireotide.[13] To our knowledge, loss of efficacy of pasireotide after its re-administration despite the initial successful response has not been reported so far. It is probable that a double mutation or a polymorphism of *USP8* or/and *EGFR* gene may explain why pasireotide was ineffective after its re-administration.

Moreover, similarly to other somatostatin analogs when used in the treatment of neuroendocrine tumors, exposure to pasireotide may probably induce SSTR desensitization via two mechanisms: SSTR internalization and downregulation on tumor cells and/or upregulation of binding sites leading to loss of recognition of SSA.[9] If other mechanisms, such as production of antibodies against pasireotide could be responsible for the escape of its effectiveness after re-administration, it remains to be elucidated.

Conclusions

In conclusion, pasireotide is a promising novel treatment for CD. The favorable effects of pasireotide are observed within a short period of time after the initiation of treatment with a remarkable biochemical control of the disease and mainly with a significant improvement of quality of life of the patients. However, an escape from the initial successful response may be observed thereby limiting long-term efficacy of this treatment.

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