Review article

Cushing's disease: is pasireotide LAR a breakthrough in adjuvant therapy after unsuccessful surgery?

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ABSTRACT

Cushing's disease is a rare endocrine disorder caused by ACTH-secreting pituitary adenoma. The treatment of choice is a transsphenoidal surgery performed by an experienced neurosurgeon. However, in some patients adjuvant treatment is required due to ineffective surgery or disease recurrence. This article discusses new aspects of pharmacological treatment of ACTH-dependent hypercortisolism in light of a recent publication reporting the efficacy and safety of once a month pasireotide LAR injections in Cushing's disease.

Key words: pasireotide, cortisol, corticotrophin, Cushing's disease, diabetes

INTRODUCTION

Cushing's disease is the most common cause of endogenous hypercortisolism. It is caused by pituitary adenoma, composed of corticotropes, and secreting corticotropin (ACTH). Under physiological conditions, corticotropin stimulates the secretion of cortisol by adrenal cortex, but its production remains under tight control of the negative feedback loop. In Cushing's disease, secretion of ACTH, as well as cortisol, is inadequate to the needs of the body, and escapes the physiological control mechanisms [1–3].

Excessive cortisol secretion in Cushing's disease leads to characteristic changes in the patient's appearance, including facial plethora and wide red abdominal striae. The adipose tissue is redistributed, being deposited on the nape of the neck and abdomen, while absent from buttocks and limbs. Increased catabolic processes lead to a reduction in the muscular tissue content and to muscle weakness. Gradually, a number of complications set in, including obesity or being overweight, pre-diabetes and diabetes, arterial hypertension, coagulopathy, reduced bone mineral density, frequent infections, and depression. Untreated or improperly treated hypercortisolism caused by Cushing's disease decreases the patient's quality of life, and reduces patient survival. It is estimated that 50% of the inadequately treated patients die after 5 years [1–3].

SURGICAL TREATMENT OF CUSHING'S DISEASE

It is generally agreed that the treatment of choice in Cushing's disease is surgical removal of pituitary adenoma, i.e. transsphenoidal selective adenomectomy, performed by an experienced neurosurgeon. The efficacy of surgical treatment (surgical remission) ranges from 60% to 90%, and is the highest in the case of microadenomas that have been accurately localised in preoperative MRI scans. The efficacy is lower, though, for macroadenomas, which are rare in Cushing's disease, and it is the lowest in the case of unclear radiological image. It is worth noting that even if postoperative remission is achieved, a long-standing postoperative follow-up is necessary due to the high incidence of disease recurrence, amounting to 15–20% within 20 years from surgery [1–3].

ADRENAL STEROIDOGENESIS INHIBITORS

Pharmacological treatment of Cushing's disease is never ideal, and may never lead to remission. It should thus be administered as adjuvant therapy, following an ineffective surgical procedure, inability to localise the tumour during the exploration of sella turcica or when second surgery is impossible or contraindicated. It may also be indicated in cases of severe hypercortisolism as an element of patient preparation for surgical treatment, as it reduces disease symptoms and complications [2, 3].

Adrenal steroidogenesis inhibitors have been used in the adjuvant treatment of Cushing's disease for many years. They include drugs such as ketoconazole, metyrapone and mitotane, which inhibit cortisol synthesis in adrenal cortex on different stages, and in many cases may bring improvement with respect to the clinical symptoms of hypercortisolism. However, the drugs do not target the cause of the disease, i.e. the ACTH-secreting corticotrophic pituitary adenoma [2, 3].

TREATMENT ORIENTED ON THE CORTICOTROPHIC TUMOUR

In 2009, Pivonello et al. have reported that the use of selective agonist of type 2 dopaminergic receptors, cabergoline, may improve treatment outcomes in patients with Cushing's disease, following ineffective surgical treatment. However, the improvement, reflected in a significant decrease in urinary free cortisol level, was observed only in 1/3 of patients with less severe disease symptoms, and only when high doses (7 mg/week) of cabergoline were administered [4].

A significant progress in medical therapy was reported in 2012, when the results of a multi-centre clinical trial about the impact of multi-receptor somatostatin analogue, pasireotide (SOM230B), on reduction in urinary free cortisol levels in patients with Cushing's disease were published. It was reported that the use of that second generation somatostatin analogue leads to (via receptors SSTR1, SSTR2, SSTR3 and SSTR5) an inhibition in the secretion of ACTH by the corticotrophic pituitary tumour, and consequently to a significant reduction in urinary free cortisol level, which was the study's primary endpoint. The study involved pasireotide dosed at 600 to 900 μg/24 hr in 2 divided doses, administered in the form of subcutaneous injections. Shortly afterwards, pasireotide was registered in the USA and European Union for the treatment of persistent Cushing's disease as the very first medical agent directly targeting the autonomous cells of corticotroph pituitary adenoma [5].

A detailed analysis of the study results indicates, however, that even though in most patients urinary free cortisol levels were reduced, the parameter (considered a standard in the diagnostics and follow-up of hypercortisolism) normalized only in around 15% of patients treated with the dose of 600 μg/24 hr, and in 25% of those who received the dose of 900 μg/24 hr. It goes to show that the new drug, which may be used as an adjuvant treatment

of Cushing's disease (targeting the site responsible for ACTH oversecretion), is not ideal for all patients [5].

Analysis of the safety profile of short-acting pasireotide demonstrated that its strong inhibition of somatostatin receptors leads to deteriorated carbohydrate metabolism parameters in most (73%) of the patients involved. It is an important finding, as hypercortisolism in the course of Cushing's disease is in itself associated with an increase in insulin resistance and insulin secretion disorders. It is estimated that up to 70% of patients with Cushing's disease present with carbohydrate metabolism disorders at the time of diagnosis, fulfilling the criteria of prediabetes or diabetes secondary to hypercortisolism. Thus, starting them on a drug that additionally reduces the pancreatic secretory reserve may result in a decompensation of the previously diagnosed diabetes or in the progression of prediabetes to diabetes. In the above mentioned study, it was necessary to start with a new anti-diabetic medication in 45% of the study subjects. Therefore, in light of the study results, it appears best to optimise carbohydrate metabolism management, before the initiation of pasireotide therapy, with subsequent follow-up/self-monitoring of blood glucose levels, and (if needs be) a quick therapeutic intervention aimed at increasing the dose or adding a new drug to the anti-diabetes treatment regime. As regards other adverse events, a mild increase (< 3 × ULN) in aminotransferase activity was observed in 30% of the patients, which did not require discontinuation of pasireotide therapy, and in 20% of patients with normal gallbladder ultrasound scans, cholelithiasis was diagnosed within a year from treatment initiation [5]. Both of the above mentioned adverse events are also typical of the first generation somatostatin analogues: octreotide and lanreotide.

PASIREOTIDE LAR

In October this year, was published a paper summarizing the phase 3 clinical trial on the efficacy and safety of pasireotide LAR in Cushing's disease. In contrast to short-acting pasireotide, which required twice daily subcutaneous injections performed by the patient or by the medical staff, the new formula enables administration of the drug every 4 weeks, which is much easier and more convenient for patients suffering from that devastating disease [6].

Inclusion criteria and study protocol

The study involved 150 adult patients from 19 different countries. The main inclusion criteria was Cushing's disease diagnosed in patients who were not considered candidates for surgical treatment. Thus, the study included primarily those patients who had not been surgically cured (persistent Cushing's disease) or those with disease recurrence following an initially successful surgery. There was few patients with *de novo* disease as well, who did not consent to surgical treatment, and were included in the study for that reason. A limitation of the study, which one should be aware of, when analysing its results, was the fact that qualification for treatment was made dependent on 24-hour urinary free cortisol level as ranging from 1.5 to 5 × ULN (upper limit of normal). Hence, the most severely ill patients, with very high (> 5 × ULN) urinary free cortisol, were not qualified for treatment with pasireotide LAR. At the time of qualification for the study, patients were randomized to the 10 or 30 mg dose of once every 4 weeks pasireotide LAR, which could subsequently be increased to a maximum dose of 40 mg every 4 weeks depending on the expected degree of reduction in 24-hour urinary free cortisol [6].

Efficacy of pasireotide LAR

Primary endpoint of the study was the assessment of normalization of urinary free cortisol level after 7 months into treatment. Such normalization of free cortisol in urine was observed in 42% of patients receiving the 10 mg dose every 4 weeks, and in 41% of patients on the 30 mg dose administered every 4 weeks. In 5% of patients from the 10 mg/4 weeks study arm, and in 13% of patients from the 30 mg/4 weeks group, UFC levels were reduced, but full control of the parameter was not attained. It is worth mentioning that treatment efficacy (UFC control) was higher in the group that presented with lower baseline UFC levels (< 2 × ULN; 52%) as compared with the study subjects whose baseline UFC levels were higher (2–5 × ULN; 36%). Additionally, in most patients, a decrease in systolic and diastolic arterial blood pressure, waist circumference, BMI and improvement of quality of life, measured with Cushing's Quality of Life questionnaire were reported [6].

Pasireotide LAR: safety profile and adverse events

The safety profile of pasireotide LAR was not found much different from the previously described safety profile of the short-acting formula. The most significant adverse event reported was pasireotide-induced hyperglycaemia. It affected around 70% of patients receiving the 10 mg dose, and circa 80% of those on the 30 mg dose. At the same time, the glycated haemoglobin rate (HbA1c) went up from 5.7% to 6.9% in the 10 mg/4 week group, and from 5.7% to 7% in the 30 mg/4 week group, despite the inclusion or escalation of anti-diabetic drugs in the course of the study. Other adverse events included an increased risk of cholelithiasis, typical of all somatostatin analogues, related to slower emptying of the gallbladder, and found to be dose-dependent, as its reported incidence was 20% and 45% for the

10 mg and 30 mg study arms, respectively. Additionally, diarrhoea was observed in around 40% of patients, typically receding during treatment [6].

SUMMARY

Pasireotide LAR, a second-generation somatostatin analogue, which may be administered every 4 weeks, certainly constitutes an attractive therapeutic option for a selected group of patients with Cushing's disease. Its main advantage is its dosage, every 4 weeks instead of the twice daily subcutaneous injections. However, excretion of free cortisol in urine normalizes only in ca. 40% of patients, which is a reminder to all that Cushing's disease still remains a challenge for endocrinologists and neurosurgeons alike. Still, introduction of a new drug, directed at pituitary tumour, is a marked progress in the treatment of Cushing's disease, and all the more so, given the fact that it acts exactly where the disease emerges, i.e. within the pituitary gland. Nevertheless, moderate efficacy of the drug requires a case by case approach, and possibly combination treatment involving pasireotide LAR plus adrenal steroidogenesis inhibitors and/or cabergoline to increase the likelihood of biochemical control of hypercortisolemia, and improve patient prognosis. All that, however, requires further studies. At any rate, our awareness of the high incidence of carbohydrate metabolism disorders calls for an optimization of pre-diabetes or diabetes management, before the decision about treatment with pasireotide LAR in order to minimize the risk of those metabolic disorders.

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