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EDITORIAL

How to manage pasireotide, when using as medical treatment for Cushing's disease

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Cushing's disease (CD) is associated with significant morbidity and mortality, and therefore requires early intervention applying effective treatment. Transsphenoidal surgery is clearly the first-line therapy, with remission rates between 65 and 90 % in microadenomas, but somehow lower rates <65 % in macroadenomas. Second-line therapies include repeated surgery, various forms of medical treatment, radiation, and ultimately bilateral adrenalectomy. Several compounds have demonstrated some efficacy to lower cortisol excess in CD. They can be divided by their approaches targeting either the underlying corticotropic adenoma, the adrenal gland, or the peripheral glucocorticoid receptor. Unfortunately, there is no clear consensus for any of these second-line options, when and in which order they should be applied. Larger studies comparing several lines of treatment in a randomized fashion are hindered by the rarity of the disease. However, considering the relevant recurrence rates of CD after surgery [1], combined approaches applied simultaneously or in succession are necessary in many patients. To improve morbidity and mortality, those treatment options need to be analyzed with respect to their efficacy to normalize biochemical excess, tumor proliferation, and clinical consequences of the disease including quality of life. As none of the currently available treatment options except for surgery and potentially radiation is able to cure CD, side effects especially during long-term therapy are of special interest.

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An important addition to the medical therapy of CD stems from studies investigating compounds targeting the underlying corticotropic pituitary adenoma. Although these tumors are usually small, the ERCUSYN study documented macroadenomas in 21 % of patients with CD (11 % with extrasellar extension) [2]. Pasireotide (SOM230) is a multireceptor ligand somatostatin analog with particular high affinity to the somatostatin receptor subtype 5 strongly expressed in corticotropic adenomas. In a recent phase III, randomized, double-blind, multicenter trial, 15 and 26 % of patients with CD (for the 600 and 900 μg doses, respectively, given subcutaneously bid) normalized their UFC at 6 months [3], with concurrent improvements in clinical symptoms [4, 5] and relevant reduction in tumor volume. Those effects were sustained for a period of over 24 months [6]. A subsequent report on eight patients treated with pasireotide for at least 6 months in a single center study as part of the phase III trial also indicated relevant tumor shrinkage [7]. Such antiproliferative effect may be useful in the medical management of Nelson's syndrome, as demonstrated in a recent case report [8]. Therefore, pasireotide may be especially considered in patients with relevant tumor mass and/or tumor progress, potentially also after bilateral adrenalectomy.

Before pasireotide is started, patients should be informed about the most common (frequency >10 %) side effects: diarrhea, nausea, abdominal pain, fatigue, cholelithiasis, injection side reactions, and hyperglycemia. Most resemble those well known for other somatostatin analogs, so that physicians will feel familiar to cope with them. However, the rate of hyperglycemia is clearly increased, as demonstrated in the phase III trial, with the mean HbA_{1C} increasing from 5.8 % in both the 600 and 900 μg groups at baseline to 7.2 and 7.4 %, respectively, at month 6. Therefore, patients should be monitored for

changes in glucose metabolism, especially during the first days and weeks of treatment (at least every week for the first 2–3 months and periodically thereafter), as those effects occur rapidly after treatment initiation [9]. If possible, patients should be trained in self-monitoring of glucose levels. A recent study in healthy volunteers suggests that pasireotide-associated hyperglycemia is related to decreases in insulin secretion and incretin hormone responses, without changes in hepatic/peripheral insulin sensitivity [10]. A subsequent study conducted to evaluate different antihyperglycemic drugs in the management of pasireotide-associated hyperglycemia suggested that vildagliptin and liraglutide were most effective in minimizing pasireotide-associated hyperglycemia, with little effects of metformin [11]. However, it should be kept in mind, that healthy volunteers may not resemble the typical patient with CD and relevant insulin resistance due to hypercortisolemia. For reasons of ease of application, well-characterized side-effect profile, and costs, metformin in the author's opinion should be used as first-line intervention in those patients with hyperglycemia during treatment with pasireotide, as suggested also by an expert panel [12]. If uncontrolled hyperglycaemia persists despite appropriate management, the dose of pasireotide should be reduced and further treatment with pasireotide reconsidered depending on its efficacy.

Various studies of pasireotide have revealed some other rare, but important side effects. As increases in liver enzymes may occur, monitoring of liver function is recommended after one, 2, 4, 8, and 12 weeks during treatment. However, in the majority of cases, the liver values return to normal without discontinuation of pasireotide. In rare cases of a sustained increase (ALT or AST >5 × ULN, or ALT or AST >3 × ULN combined with bilirubin >2 × ULN), treatment should be discontinued. Prolongation of the QT interval has also been described, but rarely exceeded >500 ms in CD patients (<1 %). Episodes of torsade de pointes were not recorded in any clinical study of pasireotide. However, pasireotide should be used with caution in patients who are at significant risk of developing prolongation of QT (e.g., intake of other drugs affecting QT, baseline QTcF >470 ms), and an ECG is recommended 1 week after the beginning of the treatment. Increases of QTcF to >470 ms should trigger a referral to a cardiologist, with discontinuation of pasireotide in those patients with confirmed QTcF >500 ms. As bradycardia has been reported, patients at risk due to other conditions should be monitored appropriately. Of note, pasireotide may lead to a rapid and marked decrease in cortisol levels with development of adrenal insufficiency (e.g., one patient in the author's experience with UFC and salivary cortisol levels below the detection level of the assay). Patients should be advised about the clinical signs and symptoms, and glucocorticoid replacement and/or dose reduction of pasireotide may be necessary.

Considering both the potential benefits of a pituitary-directed approach and the side effects especially with respect to hyperglycemia, early indicators of a sufficient response are clearly of interest to warrant continuous treatment. Further analysis of the initial phase III study indicated that baseline biochemical activity was associated with UFC normalization at 6 months, ranging from 50 % in patients with baseline UFC 1.5–2 × ULN, 25 % with baseline UFC >2–5 × ULN to 5 % with baseline UFC >5 × ULN [3]. Another predictive parameter may be early treatment response at 1 or 2 months. In patients with uncontrolled hypercortisolism (assessed by UFC) at those time points, hypercortisolism remained uncontrolled in 92 % at month 6 and 89 % at month 12. Changes in salivary cortisol during the days following initiation of therapy may allow for simpler assessment of early response, but need to be evaluated in larger studies [13]. Trementino et al. demonstrated that an acute pasireotide suppression test applying 600 μg subcutaneously had high accuracy to predict treatment response evaluated after 1–9 months of therapy with pasireotide 600 μg bid subcutaneously [14]. UFC normalization in this study was high with approximately 68 % and accompanied by sustained normalization of late night salivary cortisol in all and clinical improvement in all but one patient. Assessment of cortisol levels every 2 h for 8 h during initial suppression testing demonstrated relevant accuracy to predict long-term response, with a >28 % fall of cortisol resulting in 92 % sensitivity and 75 % specificity for later UFC normalization. Interestingly, a >27 % fall in late-night salivary cortisol on the day of testing compared to the day before had an even higher accuracy to predict treatment efficacy, with a sensitivity of 91 % and a specificity of 100 %. If confirmed in larger trials, such testing alone or in combination with other predictive parameters would certainly help to indicate those patients who will benefit most from a treatment with pasireotide, therefore allowing for continuous suppression of the underlying corticotropic pituitary adenoma. However, until further studies are available, it should be remembered, that the predictive value of short-term testing is still controversial for another pituitary disease after many years of investigation. While some studies have suggested an acute octreotide suppression test as a reliable tool for the selection of patients with active acromegaly who will achieve 'safe' GH levels during long-term treatment with long-acting somatostatin analogs [15, 16], others see only limited predictive value of such test [17]. Such discrepancies may be due to differences in criteria to define long-term remission, potential bias in the selection of patients followed long-term in retrospective studies, and various criteria used for the interpretation as a reliable test.

Furthermore, the time point of testing to define long-term response may be important, as continuous effects of treatment may result in an increasing response rate. Although the limited data available so far suggest maintenance rather than increases in response rates for pasireotide in CD patients during continuous treatment [6, 18], all these factors should be considered when designing further studies to analyze short-term predictive tests for pasireotide in CD.

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Compliance with ethical standards

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