Therapeutic innovations in endocrine diseases – Part 4: Pasireotide: Long-acting release somatostatin analogue

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Somatostatin and analogues: background information

Somatostatin was identified in 1973 by Roger Guillemin et al. as a hypothalamic hormone capable of slowing the pituitary production of growth hormone (GH) [1]. Somatostatin, or SRIH (somatotropin release-inhibiting hormone), is, in fact, a ubiquitous hormone, which is also produced by the endocrine cells of the pancreas, the digestive tract, the parafollicular C cells of the thyroid, the neurons of the central and peripheral nervous system, the immunocompetent cells (macrophages, monocytes) and various tumour cells. In addition, its action is expressed by inhibiting the release of corticotropin (ACTH), prolactin (PRL), thyroid stimulating hormone (TSH) and serotonin. It reduces insulin and glucagon production by the endocrine pancreas, decreases motility and excessive secretions of the gastrointestinal tract and is a nerve transmission regulator. It reduces cellular proliferation and counteracts the development of certain tumours. It is secreted in the form of 2 peptides composed of 14 and 28 amino acids (SS-14 and SS-28), as well as another peptide of 17 amino acids (cortistatin), which is more specifically produced by the cerebral cortex, kidneys, pancreas and the immune cells. They all bind to specific receptors, the genes of which were identified in 1992. The abundance, distribution and the specific functions of the 5 sub-types (SSTR1 to SSTR5) vary according to the nature of the normal or tumour tissue [2].

It quickly became apparent that the brief half-life of somatostatin (close to 2 minutes) and the lack of specificity of its action were obstacles to its therapeutic use. Shortly after the identification of the hormone, the SANDOZ research group in Basel studied the possibility of developing long-acting analogues, which could relatively maintain insulin production (to avoid diabetes mellitus) and primarily reduce the production of growth hormone. In 1980, this resulted in the synthesis of LPM-3105 (Pasireotide).

Summary

Pasireotide, the latest long-acting release somatostatin analogue, is distributed more widely to the various somatostatin receptors, which theoretically increases its strength and broadens its scope. Does this reflect genuine therapeutic progress? Or rather does its reduced specificity cause too many adverse reactions to make it a significant therapeutic achievement?
octreotide (Sandostatin®), composed of 8 amino acids and possessing a ring structure, which is essential for binding to the receptors. Its pharmaceutical dosage form was modified to further prolong the duration of its activity (Sandostatin Lar®). In the meantime, IPSEN pharmaceutical company developed lanreotide (Somatuline®), in short- and long-acting forms with similar tolerability and activity. These drugs have an inhibitory effect on the adenylyl cyclase-cAMP pathway and calcium channels, which gives them the capability of reducing hormonal and digestive secretions, cellular growth and of increasing apoptosis. The antiproliferative effect is also explained by inhibition of angiogenesis within the tumour and by indirect inhibition of growth factors and hormones with tropic action. Finally, these drugs have an effect on the modulation of the immune system [3]. Many studies have demonstrated the efficacy of these analogues in the therapeutic management of secreting pituitary adenomas (somatotropes, thyrotropes) through the reduction of hormonal secretions and the limitation of tumour progression. They have also been successfully used in carcinoid tumours, endocrine tumours of the pancreas, gastrinomas and ECL (enterochromaffin-like) tumours of the stomach and in certain meningiomas. In addition, they have been found useful in occlusive intestinal syndromes, progressive ophthalmopathy related to Graves’ disease [4,5], in migraine, bleeding related to angiodysplasia, and rupture of oesophageal varices [6]. The labelling of indium-111 pentetreotide (Octreoscan®) enabled the visualization of various tumours and inflammatory processes expressing somatostatin receptors and quantifying their affinity [2]. Octreotide and lanreotide are quite well tolerated in treatment; they sometimes cause digestive disorders however, especially subsequent to injection, but also cholelithiasis, which are explained by absence of gallbladder contraction. It appears that these two analogues have a strong binding affinity for the SSTR2 receptors (particularly expressed in the brain, anterior pituitary gland, pancreas, gastrointestinal tract, kidney), as well as the SSTR5 receptors (brain, pituitary gland, heart, gastrointestinal tract) and SSTR3 receptors (brain, pituitary gland, gastrointestinal tract), but not on the other somatostatin receptors, SSTR1 and SSTR4 [7].

It is for these reasons that Novartis pharmaceutical company has, since 2011, been developing a new analogue, known as SOM230 or pasireotide (Signifor®). It is a cyclic hexapeptide with greater affinity, and is highly binding primarily to SSTR5, as well as to SSTR1, SSTR2, and SSTR3, but not to SSTR4 [7]. Preliminary investigations have shown that it has greater power than octreotide to inhibit the secretion of growth hormone and IGF1 production [8]. In addition, pasireotide has the special feature of reducing ACTH production and thus cortisol by corticotrophic adenomas, which in fact highly express SSTR5. The main challenge involves glucose tolerance, due notably to the inhibitor effect of pasireotide on insulin secretion.

**Pasireotide and acromegaly**

Clinical investigations have demonstrated the efficacy of pasireotide in controlling the hypersomatotropism of patients with acromegaly, reducing it in approximately one-third of cases. Compared with other somatostatin analogues, pasireotide increases the risk of hyperglycaemia or diabetes mellitus, to the extent that the increase in the risk/benefit ratio does not justify its use as first-line therapy in patients with acromegaly who are naive to any medical treatment [9–11].

The role of pasireotide has been shown however to be particularly interesting in the treatment of acromegaly in patients insufficiently controlled by other somatostatin analogues, prescribed when surgery was not an option or had been unsuccessful. These somatotrophic adenomas, described as resistant, have in fact an increased expression of SSTR5 receptors [12]. In 198 patients initially taking lanreotide SR or octreotide SR with insufficient control, the effects of subcutaneous pasireotide, 40 and 60 mg daily, were evaluated. After 6 months of treatment, control of hormonal hypersecretion (GH < 2.5 µg/L and a return to normal levels of IGF1) was achieved in 15.4% of patients treated at a dose of 40 mg, and in 20% of those receiving 60 mg. About 25% of the patients treated had the IGF1 level return to normal, regardless of the pasireotide dose. A decrease or a reduction in volume of the pituitary adenoma was observed after 6 months in 70% of the evaluated patients versus 50% from the control group. The adverse reactions (diarrhoea, gallstones) were comparable. The frequency of hyperglycaemia was 33.3% and 30.6% (versus 13.6%), and that of diabetes mellitus was 20.6% and 25.8% (versus 7.6%). Glucoregulation disorders were found to be reversible after treatment discontinuation [13].

Another phase 3 study concerned patients not eligible for surgery or non-controlled after surgery. In a primary phase of 12 months, the patients received either pasireotide or octreotide SR. In a 12-month extension phase, the non-controlled patients had the possibility of receiving the comparator treatment. Therefore, of the 182 subjects taking octreotide SR for 12 months, 81 received pasireotide due to insufficient reduction of hypersomatotropism. Of these patients, about 40% stopped the treatment prematurely, mainly because of an adverse reaction (12/81). Of the patients who continued the treatment for one year, 17% (14/81) had GH (< 2.5 µg/L) and IGF1 return to normal levels, and 27% (22/81) only had IGF1 return to normal [14].

The consideration of pasireotide use can as a result be discussed in patients with unsuccessful surgery or those who are insufficiently controlled by the maximum recommended doses of octreotide or lanreotide [9–11]. The respective roles of pegvisomant and pasireotide in this indication will be determined.

**Pasireotide and Cushing’s disease**

Cushing’s disease is related to the development of a pituitary adenoma secreting the corticotropin (ACTH) that determines...
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Hypercortisolism. This serious condition, which causes high morbidity and increased mortality, has long remained without suitable medical treatment for the cause of the disease. Nevertheless, the identification of corticotropic adenomas, dopamine sub-type 2 and somatostatin sub-type 5 receptors has made it possible to consider the therapeutic use of cabergoline and pasireotide [15].

A pilot study has shown the capacity of pasireotide to return urinary free cortisol excretion levels to normal in 17% of patients with Cushing’s disease [16].

A phase 3, randomized, double-blind, multicenter study involved 162 patients with progressive Cushing’s disease (urinary free cortisol exceeding 1.5 times the upper limit of normal), which was recurrent and non-operable. The patients were treated with 2 daily subcutaneous injections of pasireotide at a dose of either 600 µg or 900 µg; this was secondarily increased by 300 µg twice daily if the urinary free cortisol had not returned to normal at 3 months. Urinary free cortisol returned to normal in 15% (12/82) of patients from the 600 µg group, and 26% (21/80) of patients from the 900 µg group. In the 2 groups of patients requiring an increase in dose, 16% and 29%, respectively, were controlled at 6 months, and 13% and 25% at 12 months. Improvement in the clinical data (weight, blood pressure, quality of life) and metabolic data (lipids) was observed in both groups. A reduction of 9.5% in the analyzable pituitary tumours in the 600 µg group, and of 43.8% in the 900 µg group was also observed. An increase in blood glucose levels was observed in 73% of patients (118/162), leading to the introduction or increase in anti-diabetic treatment in 74 of the 162 subjects, and to the discontinuation of pasireotide in 6% of cases. There were no observations of ketoacidosis-related or hyperosmolar coma. The other adverse reactions (nausea, diarrhea, biliary sludge or gallstones) were similar to those observed with the other analogues [17].

Other open-label studies confirm the efficacy of the medication even beyond 5 years. This therefore concerns treatments for patients with Cushing’s disease who cannot be cured with surgery. Besides the biliary effects (which resulted in cholecystectomy in 4% of cases), particular vigilance must be maintained for states of fatigue and arterial hypotension, possibly related to corticotropin insufficiency; these may result in a dose reduction or even suspension of the treatment. Cases of mild prolongation of the QT interval are possible but rare (2%) and have never resulted in discontinuation of the treatment [18].

The main problem is the occurrence of hyperglycaemia and diabetes mellitus, a situation to which contribute hypercorticism itself, and when taking pasireotide the reduction of insulin production and also of the intestinal glucagon-like peptide (GLP-1) that reduces the incretin effect. These glucoregulation disorders occur even in the absence of known heredity of diabetes mellitus in young subjects. They should be detected and may benefit from various medications, including metformin, insulin-secreting agents, as well as DPP-4 inhibitors (gliptins) and GLP-1 receptor agonists (liarelutide, exenatide, etc.), before possible recourse to insulin [19].

**Pasireotide: future prospective**

The long-acting release (LAR) form is already under investigation for various indications. It should ensure better compliance with the treatment, better stability of the medication levels, and a possible reduction of adverse reactions.

Combinations with pasireotide may likely strengthen the action of various cortisol-reducing medications in severe and intractable forms of Cushing’s disease. It has also been evaluated in various secreting or non-functional endocrine tumours [20]. This does not preclude the possibility that it could develop an activity superior to that of octreotide in progressive Graves’ ophthalmopathy, in which the five types of somatostatin receptors are expressed.

**Conclusion**

The final judgement concerning the use of pasireotide remains to be seen. It plays a particular role in the recurrence of certain Cushing syndromes following surgical treatment of corticotrophic adenomas, and inoperable somatotropic adenomas that are resistant to octreotide or lanreotide. Compared with other analogues, there has still not been a thorough evaluation of its antiproliferative and immunomodulating effect. Glucoregulation disorders are the main limitation to its widespread use, a situation that is important to detect and learn to manage if the medication, which is otherwise effective, has few alternatives. Other analogues will probably emerge that are more specific to each of the 5 somatostatin receptor sub-types. The roles of the antisomatostatinergic and antidopaminergic chimeric analogues also need to be determined.

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**References**


