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Pasireotide: A potential therapeutic alternative for resistant prolactinoma Pasiréotide, une alternative thérapeutique pour les prolactinomes résistants ?

Hélène Lasolle^{1,2,3}, Alexandre Vasiljevic,^{2,3,4} Françoise Borson-Chazot^{1,2}; Gerald Raverot.^{1,2,3}

1 Fédération d'Endocrinologie, Centre de Référence Maladies Rares Hypophysaires HYPO, Groupement Hospitalier Est, Hospices Civils de Lyon, Bron, F-69677, France

2 Faculté de Médecine Lyon Est, Université Lyon 1, Lyon, F-69372, France

3 INSERM U1052; CNRS UMR5286; Cancer Research Centre of Lyon, Lyon, F-69372, France

4 Centre de Pathologie et de Neuropathologie Est, Groupement Hospitalier Est, Hospices Civils de Lyon, Bron, F-69677, France

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Corresponding author:

Professor Gérard Raverot, MD, PhD

Fédération d'Endocrinologie, Groupement Hospitalier Est

Centre de Référence Maladies Rares Hypophysaires HYPO

Hôpital Louis Pradel-1er étage

59 Bd Pinel, 69677 Bron cedex France

gerald.raverot@chu-lyon.fr

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1

2 **Abstract**

3 **Context:** About 10% of prolactinomas are resistant to dopamine agonists (DAs). The
4 only alternatives for tumor and prolactin control are surgery or radiotherapy. While
5 studies on first-generation somatostatin analogs have shown no efficacy against
6 prolactinomas, no study has been conducted on the new multireceptor-targeted
7 somatostatin receptor ligand pasireotide, which presents high affinity for 5, 3, 2 and
8 1 receptor subtypes.

9 **Case description:** A 41 year-old woman presented with a macroprolactinoma
10 showing resistance to all available DAs. She was first diagnosed at 17 years old after
11 which she had undergone two incomplete debulking surgeries. Under pasireotide
12 long-acting release (LAR) treatment, plasma prolactin levels normalized and
13 symptoms disappeared within one month after initiation. The clinical benefits of the
14 monotherapy (specifically, prolactin levels within normal range and stable tumor
15 volume) were maintained for seven years. Glucose tolerance was satisfactory.
16 Pathological analysis of the tumor revealed high SSTR5 and low SSTR2 expression
17 (25 and 5% of cells respectively).

18 **Conclusion:** This is a promising first report of a patient with a DA-resistant
19 macroprolactinoma who achieved long-term control, in terms of prolactin
20 normalization and tumor volume, under pasireotide treatment alone. Pasireotide
21 could thus be an alternative in prolactinomas resistant to DA. SSTR expression
22 analysis on pathology could guide patient selection.

23
24 **Keywords:** Pituitary tumor, prolactinoma, aggressive tumor, somatostatin receptor,
25 pasireotide

26

27 **Résumé**

28 **Contexte :** Dix pour cent des prolactinomes sont résistants aux agonistes
29 dopaminergiques (DAs), offrant comme seules possibilités thérapeutiques, pour
30 contrôler la tumeur et la prolactinémie, la chirurgie ou la radiothérapie. Alors que les
31 analogues de la somatostatine de première génération n'ont pas montré d'efficacité,
32 aucune publication ne rapporte l'effet du pasiréotide, analogue de la somatostatine
33 de nouvelle génération présentant un profil d'affinités plus large, notamment pour les
34 récepteurs des sous-types 5, 3, 2 et 1.

35 **Description :** Une patiente âgée de 41 ans a été adressée pour un
36 macroprolactinome évoluant depuis l'âge de 17 ans, résistant aux agonistes
37 dopaminergiques, ayant nécessité deux chirurgies d'exérèse incomplète. Après
38 introduction de pasiréotide longue durée d'action (LAR), la prolactinémie s'est
39 normalisée en 1 mois, permettant une disparition des symptômes. L'effet
40 thérapeutique était maintenu au dernier suivi, 7 ans après l'introduction, avec une
41 stabilisation du volume tumoral et une prolactinémie normale. La tolérance glucidique
42 était correcte. L'analyse histologique de la tumeur a retrouvé une forte expression de
43 SSTR5 associée à une faible expression de SSTR2 (25 et 5 % des cellules
44 respectivement).

45 **Conclusion :** Nous rapportons le premier cas de macroprolactinome résistant aux
46 agonistes dopaminergiques, pour lequel un traitement par pasiréotide seul a permis
47 un contrôle de la prolactinémie et du volume tumoral sur le long terme. Ainsi, le
48 pasiréotide pourrait être une alternative thérapeutique dans les prolactinomes

49 résistant aux agonistes dopaminergiques. L'analyse histologique de l'expression de
50 SSTR pourrait aider à sélectionner les patients.

51

52 **Mots-clés :** Tumeur hypophysaire, prolactinome, tumeur agressive, récepteurs à la
53 somatostatine, pasiréotide

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Introduction

Prolactinomas are the most frequently encountered pituitary tumor, representing around 50% of all pituitary tumors. Dopamine-agonist (DA) therapy, especially cabergoline, is the first-line treatment and is able to normalize prolactin levels and tumor volume in most cases. However, prolactin levels cannot be normalized by conventional doses in around 10% of prolactinomas [1]. These are considered as DA-“resistant” and present more often as invasive macroadenomas [2]. A tumor size reduction less than 50% maximal diameter is more rarely used as a criterion of resistance. In cases of resistance, or more rarely of intolerance to dopamine-agonists, alternative treatments are surgery and radiotherapy. However, they may not be indicated, depending on the size, localization and firmness of the tumor. Moreover, surgical excision is not always curative, especially in case of invasive tumors, while radiotherapy exposes to side effects such as hypopituitarism.

The new multireceptor-targeted somatostatin transmembrane receptor (SSTR) ligand pasireotide is marketed for patients with acromegaly or Cushing’s disease. It can bind to G-protein coupled SSTRs of normal or neoplastic pituitary cells and inhibits hormone secretion and cell growth. Unlike first generation somatostatin analogs (lanreotide or octreotide) which bind preferentially SSTR2, pasireotide binds to multiple SSTRs with a high affinity for SSTR5 followed by SSTR2, SSTR3, and SSTR1[3].

We report here the first patient with a DA-resistant macroprolactinoma to present long-term prolactin normalization on pasireotide treatment alone.

Case-report

In 2010, a 41-year-old woman was referred to us for treatment of a DA-resistant macroprolactinoma.

She was diagnosed in 1986 with a macroprolactinoma measuring 15 mm and responsible for galactorrhea and amenorrhea. Initial plasma prolactin levels were 116 ng/mL. The pituitary and visual function assessment were normal. Bromocriptine therapy was progressively increased up to 15 mg/day. In the absence of control over plasma prolactin levels, surgical removal of the tumor was decided five years later in 1991. The pathological examination revealed a grade 2b pituitary neuroendocrine tumor (Fig. 1A) with 100% of cells expressing prolactin (Fig.1B), high mitotic count (n=4), and positive P53 expression. Ki67 index was not interpretable because of technical issues.

After an initial period of post-operative remission, her initial symptoms recurred one year after surgery. At this point, plasma prolactin levels had risen to 94 ng/mL and a CT-scan revealed a macroadenoma measuring 20 mm in the right sellar region. Bromocriptine (25 mg per day) and quinagolide (225 µg per day) separately failed to normalize plasma prolactin levels. A second partial surgery was required in 2003 to treat a third cranial nerve palsy caused by tumor regrowth that had occurred once DA had been stopped. Cabergoline treatment permitted a temporary and incomplete decrease in plasma prolactin levels which allowed a spontaneous pregnancy in 2007. The patient gave birth to a normal girl but menstruation was not restored despite a continued and intensified treatment with cabergoline up to 4.5mg per week. Plasma prolactin levels rose to 127 ng/mL while MRI showed global stability of the large right sellar residue measuring 33 mm. Moreover, this higher dose of cabergoline was badly tolerated inducing asthenia and dizziness. Radiotherapy was then proposed but refused by the patient.

Re-examination of the tumor fragment from the first surgery showed expression of SSTR5 in 25% of cells (Fig.1C) whereas only 5% expressed SSTR2 (Fig.1D). The analysis of genes *AIP* and *MEN1* revealed no mutation.

As part of a clinical trial (ClinicalTrials.gov Identifier: NCT00958841, approved by ethical committee of Hospices Civils de Lyon), pasireotide LAR was begun in October 2010 at 60 mg every 28 days. This normalized plasma prolactin levels within one month (Fig. 2) and allowed the stopping of cabergoline three months later. At this point, amenorrhea-galactorrhea had stopped and MRI revealed a global stability of tumor size with necrotic transformation suggestive for an anti-tumor effect (Fig. 2). The treatment was well tolerated without any digestive disorders. There was no diabetes mellitus, but glucose intolerance occurred as shown by HbA1C rising from 5.7% to 6.2% and fasting plasma glucose level from 0.90 to 1.20 g/L then to 1.27 g/L six months after pasireotide initiation. However, this required no pharmacological treatment and the implementation of dietary measures was sufficient.

Treatment was progressively decreased to 20 mg every five weeks. At the last follow-up seven years after pasireotide initiation, the plasma prolactin levels were maintained within the normal range and MRI showed a stable residual tumor. Tolerance was correct, fasting plasma glucose was 0.97 g/L and HbA1c was 5.7%.

Discussion

We report here the first case of a DA-resistant macroprolactinoma demonstrating a clinical and hormonal response to pasireotide treatment allowing its long-term control.

Pasireotide is a new somatostatin receptor ligand currently prescribed in patients with acromegaly, Cushing's disease and neuroendocrine tumors. Compared to lanreotide and octreotide, it has a broader binding profile and significantly higher *in vitro* affinity for SSTR 1, 3 and 5 receptors (respectively 30, 5 and 40 times), and a lower one for SSTR 2 receptors (2.5 times) [3].

The expression of somatostatin receptor subtypes has already been described in human prolactinomas [4–6] and in light of our results presented here, may justify the potential use of somatostatin analogs in the treatment of prolactinomas. Both immunohistochemistry studies, via use of a scoring system (associating % of immunopositive cells and membrane staining pattern), and mRNA studies have shown the expression of three subtypes of SSTR in human prolactinomas: SSTR1, 2 and 5. The level of expression is highly variable depending on the tumor, but all studies found higher SSTR5 expression followed by lower and variable levels of expression of SSTR2A and SSTR1 [4–6]. The expression pattern has never been associated with DA resistance, tumor size or aggressiveness [5].

A role for SSTRs in prolactin secretion is suspected. However, results from *in vitro* studies on use of somatostatin analogs in prolactinomas are inconsistent. In some studies, octreotide significantly reduced prolactin secretion of primary human prolactinoma and mixed growth hormone and prolactin (GH-PRL)-secreting cultured cells [7,8]. Other studies showed an uncertain and modest reduction of prolactin secretion and cell viability, especially using octreotide [6,9,10]. These inconsistencies could be due to differences in SSTR2 expression, as indicated by Acunzo *et al.* who observed prolactinomas becoming sensitive to octreotide only after *SSTR2* gene transfer [10,11]. Evidence suggests that pasireotide may be more effective

than other somatostatin analogs at reducing prolactin secretion. In 1999, Jaquet *et al.* demonstrated that another somatostatin agonist (BIM-23268) with high affinity for SSTR 5 could inhibit prolactin release from human prolactinomas in primary culture. This 26 to 90% reduction was higher compared to the one induced by octreotide [5]. More recently, pasireotide and octreotide effects on human prolactinoma and GH/PRL-secreting tumor were compared *in vitro*. Pasireotide could reduce PRL secretion between 38 and 74 % in GH/PRL and between 23 and 80% in PRL tumors, compared to the reduction achieved with octreotide of between 16 and 66% in GH/PRL and 0 and 30% in PRL tumors [7]. An *in vivo* study in mouse GH/PRL adenomas then showed not only a greater reduction in prolactin secretion with pasireotide compared to with octreotide but also a superior anti-tumor effect [12]. However, the effects of pasireotide did not differ significantly from octreotide in other recent studies [6,8,9]. Moreover, in these latter studies, the effect of somatostatin analogs on prolactin secretion was weaker than that of DAs, even in prolactinomas considered as resistant [5–7].

As suggested by *in vitro* studies, the SSTR profile of prolactinomas may explain the mainly disappointing results of first generation somatostatin analogs in treating prolactinomas. Only one successful case of octreotide treatment has been reported [13] in a young man who had previously undergone two surgical excisions. Initiation of octreotide at 20 mg every 28 days in association with cabergoline led to normalized plasma prolactin levels at the 12 month follow-up and stability of the pituitary tumor at 2 years, as shown by MRI. All other studies using cyclic synthetic somatostatins or octreotide reported therapeutic failures [14].

Clinical effects of the second-generation somatostatin analog pasireotide on prolactinomas have not yet been reported in the literature. Our report demonstrates the efficacy of pasireotide to normalize prolactin secretion, achieve long-term control over tumor

173 volume and restore the menstrual cycle in a woman with a resistant prolactinoma ineffectively
174 treated over the previous 24 years with high doses of all available dopamine agonists
175 (bromocriptine, quinagolide, cabergoline). In such cases of DA-resistant prolactinoma, this
176 treatment could be proposed before considering radiotherapy or temozolomide treatment
177 options.

178 No significant adverse effects of pasireotide were observed in this patient. Digestive disorders
179 and hyperglycemia are usually the most frequent adverse effects of this drug. As pasireotide is
180 associated with a reduction in the secretion of the hormones insulin and incretin,
181 hyperglycemia and diabetes are observed in 30% of acromegalic patients and up to 70% of
182 patients with Cushing' disease. However, the glucose tolerance disturbance induced by the
183 IGF1 and cortisol excess likely potentiates the hyperglycemia occurring under pasireotide. A
184 lower rate of hyperglycemia events should be expected in patients with prolactinoma.

185 In acromegalic patients, the relation between SSTR subtypes expression by
186 immunohistochemistry and response to somatostatin analogs is suggested [15,16]. Our results
187 support this hypothesis in prolactinomas for which SSTR5 expression is significant. SSTR
188 subtype expression profile could therefore potentially guide therapeutic choice and allow a
189 personalized therapy for these rare patients.

190 In conclusion, our case has demonstrated the potential role of pasireotide for treating DA-
191 resistant macroprolactinomas. SSTR expression may guide the choice of therapy. However,
192 pasireotide being quickly efficient, administration as a short therapeutic test may be sufficient
193 to identify potential responders.

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197 **Patient consent**

198 The author confirm that informed consent has been obtained from the patient for publication
199 of the case report and accompanying images.

200

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208

209 **Disclosure summary**

210 The authors declare that they have no competing interest.

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213 **References**

- 214 [1] Di Sarno A, Landi ML, Cappabianca P, Di Salle F, Rossi FW, Pivonello R, et al.
 215 Resistance to cabergoline as compared with bromocriptine in hyperprolactinemia:
 216 prevalence, clinical definition, and therapeutic strategy. *J Clin Endocrinol Metab*
 217 2001;86:5256–61. doi:10.1210/jcem.86.11.8054.
- 218 [2] Vroonen L, Jaffrain-Rea M-L, Petrossians P, Tamagno G, Chanson P, Vilar L, et al.
 219 Prolactinomas resistant to standard doses of cabergoline: a multicenter study of 92
 220 patients. *Eur J Endocrinol* 2012;167:651–62. doi:10.1530/EJE-12-0236.
- 221 [3] Bruns C, Lewis I, Briner U, Meno-Tetang G, Weckbecker G. SOM230: a novel
 222 somatostatin peptidomimetic with broad somatotropin release inhibiting factor (SRIF)
 223 receptor binding and a unique antiseecretory profile. *Eur J Endocrinol* 2002;146:707–16.
- 224 [4] Thodou E, Kontogeorgos G, Theodossiou D, Pateraki M. Mapping of somatostatin
 225 receptor types in GH or/and PRL producing pituitary adenomas. *J Clin Pathol*
 226 2006;59:274–9. doi:10.1136/jcp.2005.026914.
- 227 [5] Jaquet P, Ouafik L, Saveanu A, Gunz G, Fina F, Dufour H, et al. Quantitative and
 228 functional expression of somatostatin receptor subtypes in human prolactinomas. *J Clin*
 229 *Endocrinol Metab* 1999;84:3268–76. doi:10.1210/jcem.84.9.5962.
- 230 [6] Fusco A, Gunz G, Jaquet P, Dufour H, Germanetti AL, Culler MD, et al.
 231 Somatostatinergic ligands in dopamine-sensitive and -resistant prolactinomas. *Eur J*
 232 *Endocrinol* 2008;158:595–603. doi:10.1530/EJE-07-0806.
- 233 [7] Hofland LJ, van der Hoek J, van Koetsveld PM, de Herder WW, Waaijers M, Sprij-
 234 Mooij D, et al. The novel somatostatin analog SOM230 is a potent inhibitor of hormone
 235 release by growth hormone- and prolactin-secreting pituitary adenomas in vitro. *J Clin*
 236 *Endocrinol Metab* 2004;89:1577–85. doi:10.1210/jc.2003-031344.
- 237 [8] Murray RD, Kim K, Ren S-G, Lewis I, Weckbecker G, Bruns C, et al. The novel
 238 somatostatin ligand (SOM230) regulates human and rat anterior pituitary hormone
 239 secretion. *J Clin Endocrinol Metab* 2004;89:3027–32. doi:10.1210/jc.2003-031319.
- 240 [9] Ibáñez-Costa A, Rivero-Cortés E, Vázquez-Borrego MC, Gahete MD, Jiménez-Reina L,
 241 Venegas-Moreno E, et al. Octreotide and pasireotide (dis)similarly inhibit pituitary
 242 tumor cells in vitro. *J Endocrinol* 2016;231:135–45. doi:10.1530/JOE-16-0332.
- 243 [10] Cuny T, Mohamed A, Graillon T, Roche C, Defilles C, Germanetti A-L, et al.
 244 Somatostatin receptor sst2 gene transfer in human prolactinomas in vitro: impact on
 245 sensitivity to dopamine, somatostatin and dopastatin, in the control of prolactin
 246 secretion. *Mol Cell Endocrinol* 2012;355:106–13. doi:10.1016/j.mce.2012.01.026.
- 247 [11] Acunzo J, Thirion S, Roche C, Saveanu A, Gunz G, Germanetti AL, et al. Somatostatin
 248 receptor sst2 decreases cell viability and hormonal hypersecretion and reverses
 249 octreotide resistance of human pituitary adenomas. *Cancer Res* 2008;68:10163–70.
 250 doi:10.1158/0008-5472.CAN-08-1857.
- 251 [12] Fedele M, De Martino I, Pivonello R, Ciarmiello A, Del Basso De Caro ML, Visone R,
 252 et al. SOM230, a new somatostatin analogue, is highly effective in the therapy of growth
 253 hormone/prolactin-secreting pituitary adenomas. *Clin Cancer Res Off J Am Assoc*
 254 *Cancer Res* 2007;13:2738–44. doi:10.1158/1078-0432.CCR-06-2505.
- 255 [13] Fusco A, Lugli F, Sacco E, Tilaro L, Bianchi A, Angelini F, et al. Efficacy of the
 256 combined cabergoline and octreotide treatment in a case of a dopamine-agonist resistant
 257 macroprolactinoma. *Pituitary* 2011;14:351–7. doi:10.1007/s11102-008-0162-y.
- 258 [14] Bronstein MD, Knoepfelmacher M, Liberman B, Marino R, Germek OA, Schally AV.
 259 Absence of suppressive effect of somatostatin on prolactin levels in patients with
 260 hyperprolactinemia. *Horm Metab Res Horm Stoffwechselforschung Horm Metab*
 261 1987;19:271–4. doi:10.1055/s-2007-1011796.

- [15] Iacovazzo D, Carlsen E, Lugli F, Chiloiro S, Piacentini S, Bianchi A, et al. Factors predicting pasireotide responsiveness in somatotroph pituitary adenomas resistant to first-generation somatostatin analogues: an immunohistochemical study. *Eur J Endocrinol* 2016;174:241–50. doi:10.1530/EJE-15-0832.
- [16] Plöckinger U, Albrecht S, Mawrin C, Saeger W, Buchfelder M, Petersenn S, et al. Selective loss of somatostatin receptor 2 in octreotide-resistant growth hormone-secreting adenomas. *J Clin Endocrinol Metab* 2008;93:1203–10. doi:10.1210/jc.2007-1986.

Figures legends:

Figure 1: Histopathological features of the first surgical specimen (original magnification x 400)

A- On hematoxylin phloxine saffron staining, the tumor shows a diffuse growth pattern. Anisokaryosis is moderate and numerous nuclei show a prominent nucleolus.

B- The majority of neoplastic cells show typical paranuclear prolactin immunoreactivity.

C- A moderately intense membranous immunoexpression of SSTR5 is observed in 25% of neoplastic cells.

D- Only 5% of neoplastic cells show a membranous immunopositivity for SSTR2.

Figure 2: Prolactin levels and MRI evolution (four years before pasireotide initiation (2006), at pasireotide initiation (2010-MO), at 3 months after pasireotide initiation (2010-M3) and at the last follow-up (2017)).