CASE REPORT

A case of an acromegalic patient resistant to the recommended maximum GH receptor antagonist dosage

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Abstract

Background: The competitive GH receptor antagonist pegvisomant is reported to normalise IGF-1 levels in up to 97 % of acromegalic patients at a maximum dosage of 40 mg/d.

Description of Case: We present an acromegalic patient resistant to the recommended maximum GH receptor antagonist dosage. The 60-year-old male patient presenting with typical clinical signs of acromegaly has underwent multiple transsphenoidal surgeries and pituitary irradiation, while currently available pharmacological therapies for acromegaly have been exhausted.

Results: Biochemical control of the disease could only be achieved until uptitration of pegvisomant to 60 mg/d which was tolerated well.

Conclusions: The current treatment algorithm for acromegaly should be modified to treat cases of persistent and uncontrolled disease. Hippokratia. 2012; 16 (1): 80-82

Key words: acromegaly, GH receptor antagonist, resistance

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Therapy for acromegaly represents a demanding task for the physician, since a subset of patients exhibit treatment-resistant disease. According to the currently available treatment algorithm, transsphenoidal surgery is the first-line treatment for acromegaly[1]. Regarding medical treatment, three drug classes are approved: dopamine agonists, somatostatin analogues and the GH receptor antagonist pegvisomant. While dopamine agonists and somatostatin analogues bind centrally to specific tumor receptors, the GH receptor antagonist pegvisomant acts on peripheral GH receptors, blocking "proper" GH receptor dimerization to prevent GH-induced signal transduction. Pegvisomant is reported to normalise IGF-1 in up to 97 % of patients at a maximum dosage of 40 mg/d[2,3].

Description of Case

In year 1992, a 43-year-old male patient presented with gradual enlargement of the hands and feet for 20 years, visual disturbance, headache, fatigue, insulin dependent diabetes mellitus and hypertension. MRI demonstrated an infra- and intrasellar pituitary macroadenoma with invasion of the sphenoidal sinus. Laboratory examination revealed elevated levels of serum GH (40 ng/ml) and IGF-1 (860 ng/ml). Acromegaly was diagnosed.

The patient received a 6-month preoperative treatment with octreotide followed by transsphenoidal tumor resection. The histology revealed a pituitary adenoma with positive immunostaining for GH. Six years afterwards a recurrence of the primary disease was diagnosed; a 2.5 cm residual tumor was present on MRI. A 3-month treatment with octreotide-LAR was followed by a 2nd transsphenoidal surgery. Combined medical treatment with long acting octreotide and bromocriptine was initiated postoperatively.

However, the patient still suffered from the typical acromegalic habitus; serum GH (28 ng/ml) and IGF-1 (680 ng/ml) were again elevated. MRI showed intra- and parasellar remnant tumor, while visual field was intact. Medication was modified as follows: long acting octreotide in combination with cabergoline. Nine months afterwards, the patient underwent fractionated stereotactic radiation.

In the course of the disease, the patient presented with persistent elevated GH (18.5 ng/ml) and IGF-1 levels (1653 ng/ml), while his metabolic situation was inadequately controlled (type 2 diabetes mellitus with a HbA1c of 9.9 %). At this time, combination therapy was stopped and pegvisomant was started at an initial dosage of 10 mg/d (Figure 1). Only, the uptitration of pegvisomant to 60 mg/d led to an IGF-1 normalization for the

first time (118 ng/ml); even a further decrease in serum IGF-1 levels was achieved (51 ng/ml). MRI revealed no significant change of the parasellar residual tumor under pegvisomant treatment.

Several measurements of pegvisomant at different time points revealed high serum levels of pegvisomant, thus assuring the patient's compliance. Serum concentrations of pegvisomant were determined by an immunofluorometric sandwichtype assay which involves two monoclonal antibodies raised against hGH, but retaining high cross-reactivity with pegvisomant[4].

Pegvisomant treatment was generally well tolerated. Mild transaminase elevation (once the upper limit of normal) occurred 30 weeks after the start of pegvisomant while biliary sludge was sonographically suspected at the time. During continued treatment, transaminases returned to normal.

The patient presented with complete anterior pituitary deficiency receiving replacement therapy with hydrocortisone, thyroxine and testosterone. Type 2 diabetes mellitus was treated with a combination of short-acting (regular) insulin, 24-hour insulin glargin and metformine.

In order to reduce the high costs of pegvisomant monotherapy, pegvisomant was reduced to 50 and 40 mg/d. IGF-1 as well as HbA1c increased again (Figure 2). The patient continued suffering from acromegalic symptoms and severely reduced quality of life. For the additional purpose of tumor shrinkage, a combination treatment of long acting octreotide 20 mg/4 weeks and pegvisomant 40 mg/d was initiated. The treatment was uptitrated to 30 mg/3 weeks of long acting octreotide and 50 mg/d of pegvisomant. Thus, serum IGF-1 levels failed to normalise (306 ng/ml) and a repeated uptitration of pegvisomant is planned again.

The medical history of the patient is shown in Table 1.

Discussion

We report an acromegalic patient resistant to multiple therapies for acromegaly, even to the recommended maximum GH receptor antagonist pegvisomant dosage. Only the uptitration of pegvisomant to 60 mg/d normalised IGF-1 levels for the first time. No adverse side effects occurred.

Our results suggest that pegvisomant uptitration might be feasible up to 60 mg/d and sometimes even necessary to normalise IGF-1 levels in cases of persistent and uncontrolled acromegaly. This dose of pegvisomant has been previously reported by Drake et al.[5]. Until which dosage this remains safe, is unknown.

A possible reason might be the fact that the number of available GH receptors at the cell surface of this patient's liver is increased to a level that demands an exceptionally

Table 1: Patients medical history.

	43-year-old male patient presenting with arthrosis, headache, carpal tunnel syndrome, sleep apnea, hyperhidrosis, pain, diabetes mellitus, thyroid goiter and organomegaly
Okt. 92	Diagnosis acromegaly
Okt. 92 - Apr. 93	Octreotide preoperatively
Apr. 93	1st transsphenoidal surgery of a macroadenoma with invasion of the sphenoidal sinus
Jun. 05	Recurrent disease
Jan. 99 - Apr. 99	Octreotide LAR (20 mg/4 weeks)
Apr. 99	2nd transsphenoidal surgery
Oct. 99 - Feb. 00	Octreotide LAR (20 mg/2 weeks) + bromocriptine (3 x 2.5 mg/d)
Feb. 00	Octreotide LAR (30 mg/3 weeks) + cabergoline (uptitration to 0.5 mg/d)
Nov. 00 - Jan. 01	Fractionated stereotactic radiation (50.4 Gy)
Jul. 03	Octreotide LAR to 30mg/3 weeks + cabergoline 1mg/d; patient still suffers severely from acromegalic comorbidities
Jul. 03	Pegvisomant, starting dose 10 mg/d, uptitration to 60 mg/d according to Figure 2
Sep. 06	Under pegvisomant reduction to 50mg/d and 40 mg/d, increasing IGF-1 levels and HbA1c; patient suffers from acromegalic symptoms; octreotide LAR 20mg/4 weeks + pegvisomant 40 mg/d
Feb. 08	Uptitration of octreotide LAR to 30mg/3 weeks + pegvisomant 50 mg/d
May 08	Pegvisomant dosage split (30-0-20 mg/d)
Apr. 09	Serum IGF-1 levels failed to normalise (306 ng/ml)

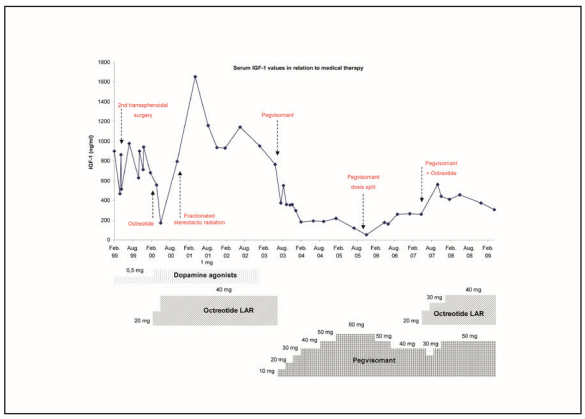

Figure 1:
Serum IGF-1 values in relation to medical therapy. In the bottom panel medical therapy with dopamine agonists (stippled area), octreotide LAR (hatched area) and pegvisomant (plaid area) is shown. Please note: Not all IGF-1 values were measured using the same assay; the DPC Immulite assay was used since 01.07.2006.

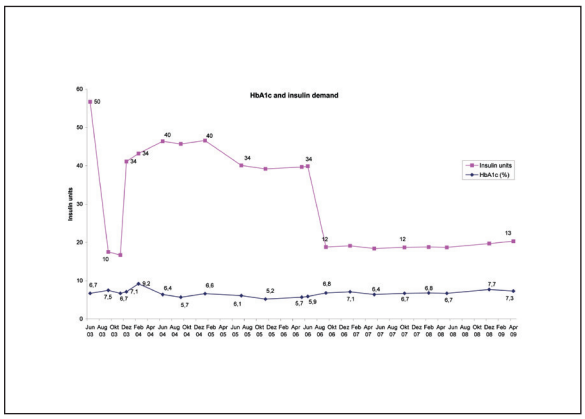

Figure 2:
HbA1c and insulin demand during the course of treatment. Considerable improvement of insulin sensitivity and glucose tolerance under pegvisomant therapy (since July 2003) indicated by significantly lower insulin unit demand. Worsening of glucose metabolism indicated by a higher HbA1c since initiation of a combination therapy with octreotide and pegvisomant (May 2007).

great amount of pegvisomant to block GH action. This might be due to the prevalent diabetes mellitus which could lead to an increase of GH receptors on the liver level as discussed by van der Lely et al. previously[6].

Additionally, we observed a considerable improvement of insulin sensitivity and glucose tolerance under pegvisomant therapy. This is the known beneficial side effect of pegvisomant on hyperglycemia and insulin sensitivity resulting from the direct anti-insulin effects by lowering GH or blocking its activity[7].

In conclusion, not only for octreotide, but also for pegvisomant, drug resistance can occur. The treatment algorithm should be adequately modified to cover these situations and patients.

Conflict of Interest

G.K.S. received lecture fees from Pfizer Pharma GmbH, Karlsruhe, Germany, Novo Nordisk Pharma GmbH, Germany, Ipsen International GmbH, Germany and Novartis Pharma GmbH, Germany. C.S. received lecture fees from Pfizer Pharma GmbH, Karlsruhe, Germany, and Novartis Pharma GmbH, Germany. MB has received lecture fees and research support from Pfizer, IPSEN and Novartis.

References

1. Melmed S, Colao A, Barkan A, Molitch M, Grossman AB, Kleinberg D, et al. Guidelines for acromegaly management: an update. J Clin Endocrinol Metab. 2009; 94: 1509-1517.
2. Kopchick JJ, Parkinson C, Stevens EC, Trainer PJ. Growth hormone receptor antagonists: discovery, development, and use in patients with acromegaly. Endocr Rev. 2002; 23: 623-646.
3. Trainer PJ, Drake WM, Katznelson L, Freda PU, Herman-Bonert V, van der Lely AJ, et al. Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. N Engl J Med. 2000; 342: 1171-1177.
4. Colao A, Pivonello R, Auriemma RS, De Martino MC, Bidlingmaier M, Briganti F, et al. Efficacy of 12-month treatment with the GH receptor antagonist pegvisomant in patients with acromegaly resistant to long-term, high-dose somatostatin analog treatment: effect on IGF-I levels, tumor mass, hypertension and glucose tolerance. Eur J Endocrinol. 2006; 154: 467-477.
5. Drake WM, Berney DM, Kovacs K, Monson JP. Markers of cell proliferation in a GH-producing adenoma of a patient treated with pegvisomant. Eur J Endocrinol. 2005; 153: 203-205.
6. van der Lely AJ, Kopchick JJ. Growth hormone receptor antagonists. Neuroendocrinology. 2006; 83: 264-268.
7. Clemmons DR, Chihara K, Freda PU, Ho KK, Klibanski A, Melmed S, et al. Optimizing control of acromegaly: integrating a growth hormone receptor antagonist into the treatment algorithm. J Clin Endocrinol Metab. 2003; 88: 4759-4767.