Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 58; Numer/Number 4/2007
ISSN 0423–104X

The medical treatment of acromegaly

Leczenie farmakologiczne akromegalii

Aart-Jan van der Lely

Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands

Abstract

Acromegaly can be treated with several medical modalities. The growth hormone (GH) receptor antagonist pegvisomant, in particular, is able to reduce serum insulin-like growth factor I (IGF-I) concentrations to almost any desired level. Along with this important achievement come other practical issues. The most important is that IGF-I also has metabolic actions, especially the control of serum glucose concentrations. As somatostatin analogues and pegvisomant have their own intrinsic differential effects on serum GH levels and actions as well as on serum IGF-I levels and actions, it should not automatically be assumed that absolute concentrations of these parameters of disease activity reflect the same levels of action. In the ideal situation we should be able to develop treatment of specific target levels for both GH and IGF-I that might even be patient-specific as well. To date we have not moved as far as this, but awareness of treatment-specific differential effects might help us to understand some of the signs and symptoms that we encounter in acromegalic patients.

(Pol J Endocrinol 2007; 58 (4): 361–363)

Key words: *acromegaly, somatostatin analogues, growth hormone receptor antagonist, glucose and insulin metabolism*

Streszczenie

W akromegalii możliwe są różne sposoby farmakoterapii. Antagonista receptora hormonu wzrostu (GH, *growth hormone*) — pegvisomant powoduje obniżenie stężenia insulinopodobnego czynnika wzrostu-I (IGF-I, *insulin-like growth factor I*) do oczekiwanych wartości. Następstwem tego efektu jest wiele praktycznych konsekwencji. Najważniejsze jest to, że działanie metaboliczne IGF-I odgrywa szczególną rolę w regulacji stężenia glukozy. Podobnie do analogów somatostatyny pegvisomant wykazuje własny wewnętrzny zróżnicowany wpływ na stężenia w surowicy oraz działania GH i IGF-I. Na tej podstawie nie można automatycznie zakładać, że stężenia tych wskaźników aktywności choroby odzwierciedlają taki sam poziom ich działania. W idealnej sytuacji powinna istnieć możliwość rozwoju specyficznej terapii celowanej, ukierunkowanej na poziomy zarówno GH i IGF-I, które mogłoby równocześnie być specyficzne dla pacjenta. Obecnie, nie dysponujemy jeszcze takimi osiągnięciami, ale realizacja typowych dla terapii zróżnicowanych efektów mogłaby pomóc nam zrozumieć niektóre objawy, które stwierdza się u chorych na akromegalię.

(Endokrynol Pol 2007; 58 (4): 361–363)

Słowa kluczowe: *akromegalia, analogi somatostatyny, antagonista receptora hormonu wzrostu, metabolizm glukozy i insuliny*

As all the available medications for the treatment of pituitary tumours were introduced more than 10 years ago except for the medical possibilities for treating somatotropinomas, this section only addresses the achievements that have been made in controlling the signs and symptoms of acromegaly.

Prof. Aart-Jan van der Lely
Head of Section of Endocrinology
Dept. of Internal Medicine. Erasmus University Medical Center,
3000 CA Rotterdam, 's Gravendijkwal 230
The Netherlands
phone: + 31 10 463 28 62, fax: + 31 10 463 36 39
e-mail: a.vanderlelij@erasmusmc.nl

Somatostatin analogues

The medical treatment modalities available for acromegaly are the dopamine-agonists (bromocriptine, quinagolide and cabergoline) and somatostatin analogues (octreotide and lanreotide). Dopamine agonists have limited efficacy and tolerability and are, in general, less effective than the somatostatin analogues [1, 2]. Long-acting somatostatin analogues are given every two to

four weeks and normalise serum IGF-I levels in about 65% of patients [3, 4]. This still leaves at least one third of patients eligible for a more effective medical therapy. Somatostatin analogues have been and are used for acromegalic individuals to suppress GH secretion; however, they also inhibit TSH, insulin, glucagon and neuropeptide secretion.

Pegvisomant

GH is normally cleared via the kidneys and/or GH receptor (GHR) internalisation and has a half-life of approximately 15–20 minutes. Pegvisomant is a GH analogue that includes a single amino acid substitution (lysine for glycine) at position 120, which, alone, generates the GH antagonist. Additional changes include amino acid substitutions within binding site 1 (which are thought to increase the affinity of the molecule to the GHR) and a further modification by the addition of polyethylene glycol moieties that increase the half-life and reduce the immunogenicity of the molecule. Interestingly, recent data has shown that the eight amino acid substitutions in Site 1 do not actually increase the binding affinity of the molecule to the GHR. However, the eight amino acid substitutions remove two potential sites for PEG addition, namely at Lys^{168} and Lys^{172}, which are within the native binding Site 1 [5]. Furthermore, these eight additional mutations in Site 1 do not interfere with the preformed receptor dimer or receptor internalisation [5].

Following GH binding to the GHR, the complex is internalised [6–9]. However, pegvisomant cannot transduce intracellular GH-specific signals. Pegvisomant does not inhibit dimer formation but prevents "proper" or functional dimerisation of the GHR [10].

The clinical use of pegvisomant in acromegaly

Several important studies have established the efficacy of long-term pegvisomant therapy in the treatment of acromegaly [11–13]. In a double-blind placebo-controlled study 112 patients with active acromegaly were treated with either placebo or one of three subcutaneous dosages (10, 15 or 20 mg) of pegvisomant for 12 weeks [12]. Parameters for the efficacy of pegvisomant were serum IGF-I and GH concentrations, as well as a questionnaire evaluating soft-tissue swelling, arthralgia, headache, excessive perspiration and fatigue. In the pegvisomant-treated patients a dose-related improvement in symptoms and signs was observed. Serum IGF-I concentrations decreased significantly in all treatment groups, and 82% of patients treated with the highest dose achieved normal serum IGF-I concentrations at the end of the study. Although pegvisomant seemed a very effective drug for the treatment of acromegaly [12], questions concerning its safety and efficacy in the long term remained [14]. In one patient with a clinically important increase in tumour-size under pegvisomant monotherapy, co-treatment with octreotide halted further tumour growth and resulted in a synergistic decrease in serum IGF-I concentrations [15]. Daily subcutaneous administration of pegvisomant is thus the most effective medical treatment for acromegaly to date. The rationale for using a combination of somatostatin analogues and pegvisomant is based on the assumption that less pegvisomant is needed when there is less endogenous GH with which to compete. Indeed, because of the presence of high concentrations of somatostatin analogue in serum and unlike what can be observed during pegvisomant monotherapy, the combined treatment of a somatostatin analogue with pegvisomant is not accompanied by an increase in serum GH concentrations.

Another rationale for the combination therapy is that somatostatin decreases insulin secretion [16–20]. Portal insulin up-regulates hepatic GHR biosynthesis in a concentration-dependent manner. As GHR translocation to the cellular surface is suppressed by insulin, GHR surface availability will be the net result of these divergent effects [21]. Therefore lower portal vein insulin levels due to somatostatin analogue therapy will decrease the number of available GHR at the cell surface of the liver. This implies that the efficacy of the GHR antagonist pegvisomant is likely to be increased by the presence of a somatostatin analogue for two reasons: the first is that the level of endogenous GH is reduced since somatostatin analogues inhibit GH secretion by the pituitary adenoma, while the second is that somatostatin analogues reduce the number of GHR in the liver by reducing insulin secretion so that the liver becomes relatively GH-resistant. Together, these mechanisms reduce the amount of pegvisomant that is necessary to block GH action in order to normalise the serum total IGF-I concentration. Indeed, Feenstra et al. observed that combined treatment with monthly long-acting somatostatin analogue injections and weekly subcutaneous pegvisomant injections is a rational medical treatment combination [22]. This therapy seems to be safe and effective in normalising serum IGF-1 concentration in more than 90% of patients with active acromegaly who cannot be controlled with long-acting somatostatin therapy alone. This efficacy rate is equal to the efficacy of pegvisomant monotherapy. In their study no increase whatsoever in pituitary tumour volume could be observed in any of the patients, which might indicate that with respect to pituitary tumour size combined therapy is safer than pegvisomant monotherapy. The

combined therapy might induce mild disturbances in liver function tests, however.

In conclusion, pegvisomant is the first member of a new class of drugs against acromegaly. It seems to have exhibited hardly any side-effects to date, although data on long-term safety still need to be gathered. Potential improvement in efficacy and perhaps even safety with regard to tumour size may be gained from the combination of somatostatin analogues and pegvisomant.

Reference

1. Abs R, Verhelst J, Maiter D et al. Cabergoline in the treatment of acromegaly: a study in 64 patients. J Clin Endocrinol Metab 1998; 83 (2): 374–378.
2. Jaffe CA, Barkan AL. Treatment of acromegaly with dopamine agonists. [Review]. Endocrinol Metab Clin North Am 1992; 21: 713–735.
3. Chanson P, Boerlin V, Ajzenberg C et al. Comparison of octreotide acetate LAR and lanreotide SR in patients with acromegaly. Clin Endocrinol (Oxf) 2000; 53 (5): 577–586.
4. Chanson P, Leselbaum A, Blumberg J et al. Efficacy and tolerability of the long-acting somatostatin analog lanreotide in acromegaly. A 12-month multicenter study of 58 acromegalic patients. French Multicenter Study Group on Lanreotide in Acromegaly. Pituitary 2000; 2 (4): 269–276.
5. Ross RJ, Leung KC, Maamra M et al. Binding and functional studies with the growth hormone receptor antagonist, B2036-PEG (pegvisomant), reveal effects of pegylation and evidence that it binds to a receptor dimer. J Clin Endocrinol Metab 2001; 86 (4): 1716–1723.
6. Maamra M, Finidori J, Von Laue S et al. Studies with a growth hormone antagonist and dual-fluorescent confocal microscopy demonstrate that the full-length human growth hormone receptor, but not the truncated isoform, is very rapidly internalized independent of Jak2-Stat5 signaling. J Biol Chem 1999; 274 (21): 14 791–14 798.
7. Govers R, ten Broeke T, van Kerkhof P et al. Identification of a novel ubiquitin conjugation motif, required for ligand-induced internalization of the growth hormone receptor. EMBO J 1999; 18 (1): 28–36.
8. Veldhuis JD, Bidlingmaier M, Wu Z et al. A selective recombinant human (rh) GH-receptor antagonist fails to impede metabolic removal of endogenous or exogenous GH in healthy adults: evidence that the GH receptor does not participate primarily in the in vivo GH elimination process. 11th International Congress of Endocrinology 2000, Sydney, Australia, P405. (Abstract).
9. Ross RJ, Leung KC, Maamra M et al. Binding and functional studies with the growth hormone receptor antagonist, B2036--PEG (pegvisomant), reveal effects of pegylation and evidence that it binds to a receptor dimer. J Clin Endocrinol Metab 2001; 86 (4): 1716–1723.
10. Harding PA, Wang X, Okada S et al. Growth hormone (GH) and a GH antagonist promote GH receptor dimerization and internalization. J Biol Chem 1996; 271 (12): 6708–6712.
11. Herman-Bonert VS, Zib K, Scarlett JA et al. Growth hormone receptor antagonist therapy in acromegalic patients resistant to somatostatin analogs. J Clin Endocrinol Metab 2000; 85 (8): 2958–2961.
12. Trainer PJ, Drake WM, Katznelson L et al. Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. N Engl J Med 2000; 342 (16): 1171–1177.
13. van der Lely AJ, Hutson RK, Trainer PJ et al. Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. Lancet 2001; 358 (9295): 1754–1759.
14. Utiger RD. Treatment of acromegaly. N Engl J Med 2000; 42 (16): 1210–1211.
15. van der Lely AJ, Muller A, Janssen JA et al. Control of tumor size and disease activity during cotreatment with octreotide and the growth hormone receptor antagonist pegvisomant in an acromegalic patient. J Clin Endocrinol Metab 2001; 86 (2): 478–481.
16. van der Hoek J, de Herder WW, Feelders RA et al. A single-dose comparison of the acute effects between the new somatostatin analog SOM230 and octreotide in acromegalic patients. J Clin Endocrinol Metab 2004; 89 (2): 638–645.
17. Drake WM, Rowles SV, Roberts ME et al. Insulin sensitivity and glucose tolerance improve in patients with acromegaly converted from depot octreotide to pegvisomant. Eur J Endocrinol 2003; 149 (6): 521–527.
18. Parkinson C, Drake WM, Roberts ME et al. A comparison of the effects of pegvisomant and octreotide on glucose, insulin, gastrin, cholecystokinin, and pancreatic polypeptide responses to oral glucose and a standard mixed meal. J Clin Endocrinol Metab 2002; 87 (4): 1797–1804.
19. Presti ME, Burton FR, Niehoff ML et al. Effect of octreotide on stimulated insulin release from pancreatic tissue slices. Pancreas 1998; 16 (2): 141–147.
20. Koop BL, Harris AG, Ezzat S. Effect of octreotide on glucose tolerance in acromegaly. Eur J Endocrinol 1994; 130 (6): 581–586.
21. Leung KC, Doyle N, Ballesteros M et al. Insulin regulation of human hepatic growth hormone receptors: divergent effects on biosynthesis and surface translocation. J Clin Endocrinol Metab 2000; 85 (12): 4712–4720.
22. Feenstra J, de Herder WW, Ten Have SM et al. Combined therapy with somatostatin analogues and weekly pegvisomant in active acromegaly (Erratum in: Lancet. 2005 May; 365 (9471):1620). Lancet 2005; 365 (9471): 1644–1646.