



The medical treatment of acromegaly

Leczenie farmakologiczne akromegalii

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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.

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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 mogłyby 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.

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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 achieve-

ments that have been made in controlling the signs and symptoms of acromegaly.

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

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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 Lys¹⁶⁸ and Lys¹⁷², 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-I 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.

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