Additional metabolic effects of adding GH receptor antagonist to long-acting somatostatin analog in patients with active acromegaly

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Abstract

OBJECTIVE: Somatostatin analogs, dopamine agonists and GH-receptor antagonist – pegvisomant are used in medical therapy of acromegaly. Since pegvisomant has not antitumor effect, the combination of pegvisomant and somatostatin analog could be an attractive option. Aim of study was to assess the effects of pegvisomant and octreotide LAR treatment on GH and IGF-1 levels, and glucose tolerance in acromegaly, and to assess efficacy and tolerability of rapid (after 7 days) pegvisomant dose titration.

MATERIAL AND METHODS: Six patients (4 men, 2 women) aged 47.5 years (median) with active acromegaly, after neurosurgery failed, resistant to maximal doses of octreotide, received daily 10–20 mg pegvisomant throughout 2 weeks. They were given octreotide LAR 30 mg monthly for at least 6 months before pegvisomant therapy. Clinical symptoms, GH, IGF-1, fasting glucose and insulin levels were measured on the 0, 8th and 15th day of pegvisomant therapy. On the 8th day pegvisomant dose was titrated based on serum IGF-1 level.

RESULTS: IGF-1 levels reduced from 739 at the beginning to 418 ng/ml (medians) on the 15th day of treatment and normalized in one patient. These changes were associated with improvement of glucose metabolism. One diabetic patient could even stop insulin therapy.

CONCLUSIONS: Pegvisomant is an attractive adjuvant therapy for controlling acromegaly. Pegvisomant improves insulin sensitivity as well as glucose tolerance. The GH receptor antagonist is good option for patients with active acromegaly coexistent with disturbances of glucose metabolism, especially with diabetes mellitus. Rapid pegvisomant dose increasing to efficient or maximal is well tolerated and effective.

ORIGINAL ARTICLE

Abbreviations:
GH – Growth Hormone
GHRA – Growth Hormone Receptor Antagonist
HOMA – Homeostasis Model Assessment
IGF-1 – Insulin-like Growth Factor-1
LAR – Long Acting Repeatable
OCT – Octreotide
OGTT – Oral Glucose Tolerance Test
PEG – Pegvisomant
QUICK – Quantitative Insulin Sensitivity Check
SA – Somatostatin Analog

INTRODUCTION

Acromegaly is a rare, chronic disease characterized by excessive growth hormone (GH) secretion followed by elevated insulin-like growth factor-1 (IGF-1) levels. It is usually caused by a benign adenoma of pituitary gland which occurs in > 95% of the cases (Melmed 2006; Schreiber *et al* 2007). Typical symptoms of acromegaly are associated with chronic morbidities, such as headache and arthritis, and frequent metabolic complications including diabetes mellitus and hypertension, as well as a specific acromegalic cardiomyopathy (Holdaway *et al* 2004; Colao *et al* 2004; Serri *et al* 2004). Life expectancy is reduced by 10 years on average, predominantly due to cardiovascular disease (Rajasoorya *et al* 1994). The goal of treatment is to reverse the effects of hypersecretion of GH and to normalize production of IGF-1. Effective treatment ameliorates the symptoms and signs of disease and decreases the mortality rate (Holdaway *et al* 2004).

Transsphenoidal surgery is treatment of choice for most patients with acromegaly (Melmed 2006). The development of endoscopic transsphenoidal surgery which is minimal invasive has been reported to offer several advantages over the conventional technique such as less surgical morbidity, patient's quick recovery, fewer complications (Rudnik *et al* 2007). Currently available medical therapy includes dopamine agonists, somatostatin analogs (SA) and growth hormone receptor antagonist (GHRA) – pegvisomant (PEG), and it is possible as a primary medical therapy, presurgical procedure or when surgery fails (Paisley & Trainer 2006; Bolanowski *et al* 2006). SAs lower GH and IGF-1 in 45–65% patients and cause significant tumor shrinkage, particularly when given as primary medical treatment (Drake *et al* 2001). Although symptom relief and tumor shrinkage are obtained in many cases with SA, inadequate suppression of GH secretion is encountered in 40–50% of cases. Moreover, SAs are responsible for inhibition of insulin secretion and it can result in deterioration of glucose tolerance (Paisley & Trainer 2006; Jorgensen *et al* 2005). These drugs are also responsible for suppressing thyroid-stimulating hormone, glucagon and neuropeptide secretion (van der Lely & Kopchick 2006).

Clinical studies in acromegaly have shown that PEG is a highly effective and well-tolerated therapeutic option for disease control with a normalization rate of IGF-1 in up to 97% cases (Schreiber *et al* 2007). However, PEG does not have an antitumor effect in terms of reducing tumor size and secretion of GH. In this context the combination therapy with PEG and long-acting SA analogs could be the attractive option.

The aim of study was to assess the combined effects of pegvisomant and octreotide (OCT) LAR treatment on GH and IGF-1 levels, and glucose tolerance in acromegaly, and to assess efficacy and tolerability of rapid (after 7 days) pegvisomant dose titration.

Table 1. Characteristics of patients with acromegaly.

	Median	Quartile (25%/75%)
Age (years)	47.5	39.3/52.0
Height (cm)	176.5	164.5/181.0
Body weight (kg)	87.0	76.4/114.5
Body mass index(kg/m^2)	28.2	27.8/31.2

MATERIAL AND METHODS

Material consisted of 6 patients (4 men, 2 women) aged 37–70 years (median 47.5) with active acromegaly, after unsuccessful neurosurgery, resistant to maximal doses of octreotide therapy (characteristics in Table 1). Activity of disease was confirmed by non-suppressible to < 1 ng/ml serum GH following oral administration of 75 g of glucose and no normalization of age- and sex-matched serum IGF-1 levels. Patients received 10–20 mg of PEG (Somavert, Pfizer) daily throughout 2 weeks. On the 8th day PEG dose was titrated based on serum IGF-1 level. All patients had received a long acting OCT (Sandostatin LAR, Novartis) while PEG therapy. Clinical symptoms, GH and IGF-1 levels, and fasting glucose were measured on the 0, 8th and 15th day of PEG therapy. Concentration of HbA_1c was measured in three patients with deterioration of glucose tolerance. Safety analysis included blood count, serum alanine and aspartate transaminases activity, serum total bilirubin, creatinine, cholesterol, triglycerides, potassium and sodium concentrations, urine analysis and electrocardiogram.

OGTT was performed in all patients by measuring plasma blood glucose, GH and insulin levels in 0, 30, 60 and 120 minutes of test after 75 g oral glucose load. OGTT, hormones and other biochemical measurements, i.e. lipid profile were performed at basal time, after one week of therapy before changing of dose and after two weeks of therapy. Patients received PEG in the initial dose 10 mg s.c. The dose was changed after 7 days according to normalization of IGF-1 levels. The treatment of diabetes was changed based on measurement of blood glucose level which were performed and noticed by patients. Insulin concentration was not studied in patient No 4, because he was treated by insulin at

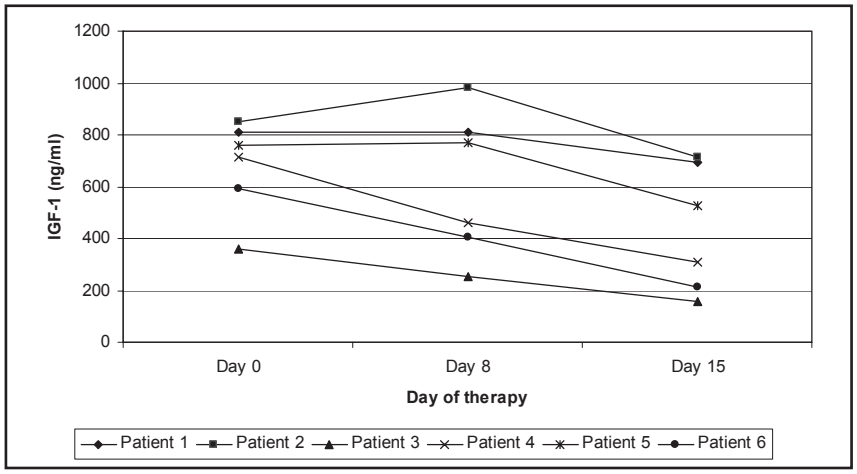

Figure 1. IGF-1 concentrations in group of 6 patients with acromegaly during pegvisomant added to somatostatin analog therapy.

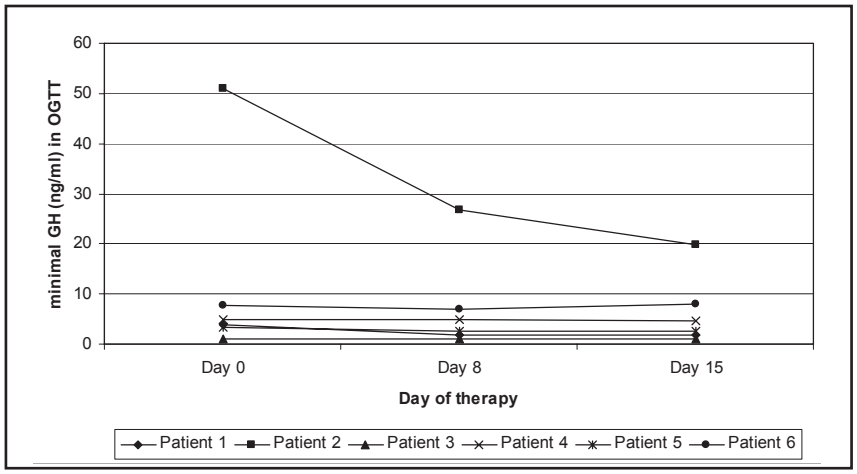

Figure 2. GH concentrations in group of 6 patients with acromegaly during pegvisomant added to somatostatin analog therapy.

Table 2. Effect of pegvisomant added to somatostatin analog treatment on minimal growth hormone in OGTT (minGH) and insulin-like growth factor-1 (IGF-1) concentrations (ng/ml).

Patient	$minGH_0$	$minGH_8$	$minGH_{15}$	$IGF\text{-}1_0$	$IGF\text{-}1_8$	$IGF\text{-}1_{15}$
Median	4.4	3.8	3.7	739.0	616.5	418.0
(quartile 25%/75%)	(3.5/6.9)	(2.1/6.4)	(2.1/7.2)	(623.0/799.5)	(417.8/801.8)	(237.3/653.5)

the beginning of the study due to diabetes mellitus. In this patient HbA_1c level was assessed at each visit.

Statistical analysis was performed by Microsoft Excel 2003 and Statistica for Windows 6.0. The effect of pegvisomant was analyzed by the Wilcoxon matched pair test (basal vs. 8 or 15 days of treatment). Data are reported as median, interval and interval quartile. P value less than 0.05 was considered statistically significant.

RESULTS

One week of PEG therapy induced reduction of IGF-1 levels in 5 patients. In the remaining patient IGF-1 level increased after one week of therapy and it was associated with increase of GH level but in the end of treatment both parameters decreased. Serum IGF-1 levels fell from a median of 739 to 418 ng/ml (p=0.0277), and normalized in one patient (Figure 1, Table 2). GH concentration also decreased during therapy and the decline was highest after one week (p=0.043; Figure 2, Table 2).

Fasting plasma glucose concentrations decreased significantly after one week of PEG treatment from median 92 to 88.5 mg/dl (p=0.046; Table 3). It returned to basal level after two weeks of treatment but the improvement of glucose metabolism was confirmed by increase of QUICK index and decrease of HOMA index. (Figures 3 and 4). Plasma insulin level was insignificantly reduced after pegvisomant therapy (7.0 vs. 5.5 μg/ml, p=0.68; Table 3). Moreover, one diabetic patient

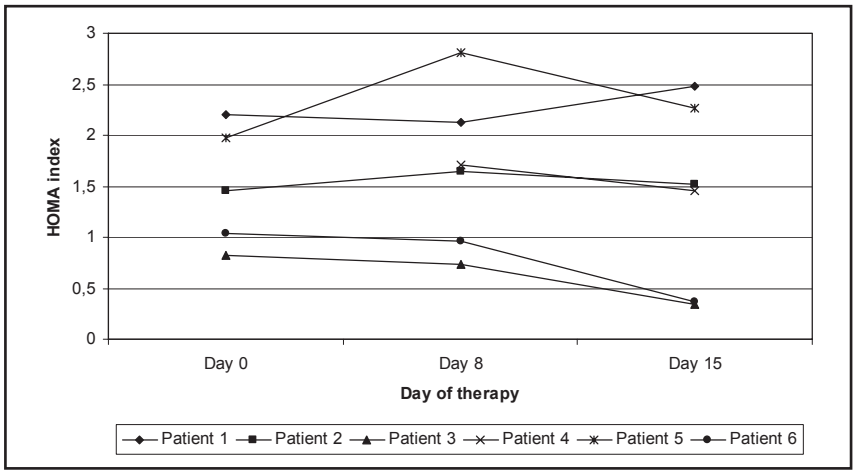

Figure 3. HOMA index in group of 6 patients with acromegaly during pegvisomant added to somatostatin analog therapy.

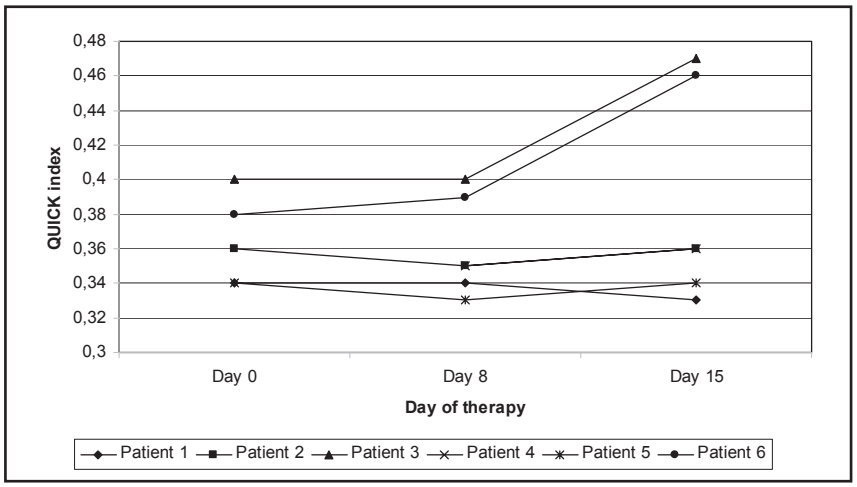

Figure 4. QUICK index in group of 6 patients with acromegaly during pegvisomant added to somatostatin analog therapy.

(No 4) could even stop insulin therapy. HbA_1c level in one diabetic patient decreased after 2 weeks from 8.1% on the day 0 to 7.7% on the day 15.

Liver and kidney function tests, as well as blood count were within normal limits at baseline and did not change during therapy. Median total serum cholesterol concentrations at baseline (211.5 mg/dl) were above the recommended level < 200 mg/dl, but did not change substantially during the course of PEG treatment (Table 4). We observed decrease in triglyceride concentrations (Table 4) in five patients and increase in one (patient No 5).

Treatment was well tolerated and no patient withdrew from study. No patient reported an injection site reaction. In one patient nausea and pain in right subabdominal region occurred, but they were not accompanied by elevation of hepatic enzymes. Therapy was not interrupted and the symptoms went away after two days.

DISCUSSION

We have shown that adding PEG to SA treatment is effective in terms of normalization of IGF-1 levels in patients with uncontrolled acromegaly while only SA given. This effect has already been observed at the low doses of PEG and increasing the dose exacerbated it. Moreover, it was linked neither to increased side effects occurrence nor their appearance. Another important finding was statistically significant fall of GH secretion on the 8th day of therapy.

An additional argument for the use of PEG is its advantageous influence on the carbohydrate metabolism. It is very important because of very frequent coexistence of acromegaly with glucose intolerance or diabetes mellitus. We observed in our study the increased QUICK index what confirmed positive PEG impact on peripheral and hepatic sensitivity to insulin. Similarly, like did Colao *et al* (Colao *et al* 2006), we observed a significant decrease in glucose levels and HOMA index, which confirmed the ability of PEG to improve glucose homeostasis and reduce insulin resistance.

Table 3. Effect of pegvisomant added to somatostatin analog treatment on glucose (GLC) and insulin (INS) concentrations (mg/dl and µg/ml, respectively).

Patient	GLC_0	GLC_8	GLC_{15}	INS_0	INS_8	INS_{15}
1	106	104	107	8,4	8,3	9,4
2	84	85	87	7,0	7,8	7,1
3	79	67	68	4,2	4,5	2,0
4	153	136	151	NA	5,1	3,9
5	98	92	98	8,2	12,4	9,4
6	86	81	74	4,9	4,8	2,0
Median (quartile 25%/75%)	92.0 (84.5/104.0)	88.5 (82.0/101.0)	92.5 (77.3/104.8)	7.0 (4.9/8.2)	6.45 (4.9/8.2)	5.5 (2.5/8.8)

NA – not assessed

Table 4. Effect of pegvisomant added to somatostatin analog treatment on total cholesterol (TCH) and triglycerides (TG) concentrations (mg/dl).

Patient	TCH_0	TCH_8	TCH_{15}	TG_0	TG_8	TG_{15}
1	263	232	268	261	153	192
2	215	191	193	139	152	127
3	192	193	184	64	42	35
4	179	192	223	198	92	154
5	239	215	215	149	174	203
6	208	171	201	102	112	81
Median (quartile 25%/75%)	211.5 (196.0/233.0)	192.5 (191.3/209.5)	208.0 (195.0/221.0)	144.0 (111.3/185.8)	132.0 (97.0/152.8)	140.5 (92.5/182.5)

Good response to PEG in patients resistant to SA treatment results from a separate mechanism of GHRA action. At this moment, an attractive concept could be combination medical therapy using SA together with PEG, which can block GH actions in target tissues. A recent study revealed that the combination of monthly OCT LAR and weekly PEG normalized IGF-1 in more than 90% patients with active acromegaly which were not controlled with SA alone (Feenstra *et al* 2005). On the contrary to other options of treatment in which the success is determined by pretreatment GH level, PEG pretends to normalize IGF-1 levels irrespective of the pre-pegvisomant serum GH/IGF-1 levels. It is connected with higher doses of GHRA but it has no influence on the safety of therapy (Parkinson *et al* 2002). It is very important because IGF-1 level is the crucial biochemical marker of the activity of the GH-IGF-1 axis, which can be used to assess the response to PEG therapy (Holdaway *et al* 2004).

Additionally, GHRA might have been useful in patients with diabetes or impaired glucose tolerance in whom SA might worsen glyceamic control. This is due to the fact that human body has also widespread expression of somatostatin receptors and consequently these agents not only lower circulating GH, but also have multiple actions on gut hormones release and glucose tolerance. Normally SA inhibit the secretion of insulin and glucagon and delay gastrointestinal glucose absorption. The combined effects of these drugs on carbohydrate metabolism in patients with acromegaly is determined by effects on GH release, which improves insulin sensitivity and inhibits insulin secretion. In contrast to this PEG is not associated with deterioration in glucose tolerance. Moreover, therapy with PEG is associated with significant reductions in insulin resistance (Parkinson *et al* 2002). It is very important because insulin resistance is a main abnormality in metabolic syndrome that is connected with increased cardiovascular mortality. Parkinson *et al* compared effect of SA and PEG treatment on the insulinogenic response to a standard meal and they revealed inhibition of insulin release by SA and consequently postprandial hyperglycaemia. On the contrary, insulin release and plasma glucose levels were not altered by PEG (Parkinson *et al* 2002). SAs in patients with acromegaly improve glucose tolerance via control of GH-IGF-1 axis, but the therapy using these drugs is associated with deterioration in glucose tolerance (Koop *et al* 1994). It was confirmed by Drake *et al*, who showed that converted therapy from OCT to PEG is connected with improvement of glucose metabolism (Drake *et al* 2003). We could observe this fact independently of influence on IGF-1 concentration.

Some authors suggested that PEG has a beneficial effect compared with OCT on glucose metabolism which is independent on GH-IGF-1 axis (Koop *et al* 1994).

CONCLUSIONS

On the basis of these results, pegvisomant is an attractive adjuvant therapy for controlling the GH-IGF-1 axis in acromegaly. Pegvisomant improves insulin sensitivity as well as glucose tolerance so it can be a good option for patients with active acromegaly coexistent with disturbances of glucose metabolism, especially with diabetes mellitus. Normalization of concentration and reduction of the severity of symptoms of the disease was already at low doses of pegvisomant. Moreover, rapid pegvisomant dose increasing to efficient or maximal is well tolerated and effective.

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