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EFFECTS OF COMBINATION THERAPY: SOMATOSTATIN ANALOGUES AND DOPAMINE AGONISTS ON GH AND IGF1 LEVELS IN ACROMEGALY

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Abstract

Background and aims. *Acromegaly is a complex endocrine disorder caused by excessive secretion of GH, secondary to a GH secreting pituitary adenoma or a mixed pituitary adenoma secreting GH and PRL.*

Methods. *The aim of this study was to evaluate the effects of combination therapy: dopamine agonist and somatostatin analogue on GH and IGF1 levels in a group of 30 patients with acromegaly. Cabergoline in a dose of 2 mg/week and 4 mg/week respectively was associated with Sandostatin LAR in a dose of 20 mg/month and 30 mg/months respectively. Eight patients were treated with Lanreotide 30 mg/week and Cabergoline 2 mg/week and 3 patients were treated with Bromocriptine 10 mg/day and Sandostatin LAR 30 mg/month.*

Results. *Combination therapy: Cabergoline and Sandostatin achieved normal levels of IGF1 in 32% of the patients, better results being obtained after 12 months of treatment in the group treated with 4 mg Cabergoline/week. In 37% of cases the levels of IGF1 decreased by 50% after 12 months of treatment. In the group treated with Cabergoline and Somatuline a normal level of IGF1 was achieved in 25% of patients after 12 months of treatment. The outcome for the group treated with Sandostatin and Bromocriptine was similar to that obtained under Cabergoline 2 mg/week. There was no significant correlation between the level of GH and the type or dose of dopamine agonist used.*

Conclusions. *In conclusion, combination therapy consisting of dopamine agonist and somatostatin analogue achieves a significant reduction of IGF1 levels in patients with mixed adenomas secreting GH and PRL. A decrease in IGF1 levels is directly correlated with the dose of Cabergoline used.*

Keywords: acromegaly, cabergoline, prolactine, insulin-like growth factor 1

Background and aims

Acromegaly is a complex endocrine disorder caused by excessive GH (growth hormone) secretion, starting after completion of puberty and closure of the epiphyseal growth plates. In over 95% of cases, the main cause of the disease is a GH-secreting pituitary adenoma or a mixed GH and PRL (prolactin) -secreting adenoma [1]. Very rarely, acromegaly is seen as part of MEN I syndrome (multiple endocrine neoplasia) or as

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a consequence of paraneoplastic GH secretion. In time, acromegaly is associated with increased morbidity and mortality due to aggregation of cardiovascular risk factors such as hypertension, diabetes mellitus and dyslipidemia [2]. Large retrospective studies have showed an *average* 10-year *reduction* in *life expectancy* in untreated patients and a twofold increase in mortality due to cardiovascular, cerebrovascular, metabolic or respiratory comorbidities [3]. Posttreatment reduction of GH levels to less than 2.5 ng/ml and normalization of serum IGF1 (Insulin-like growth factor 1) is associated with mortality rates similar to the general population [4].

The currently available treatment options for acromegaly are pituitary surgery, medical therapy and radiotherapy. Medical therapy involves the administration of somatostatin analogues, dopamine agonists or GH receptor antagonists, alone or in combination. Dopamine agonists have proved effective in mixed GH and PRL-secreting pituitary adenomas or GH-secreting tumors that express dopamine receptors. Monotherapy has a relatively low response rate of less than 15%. In patients with a partial response to somatostatin analogue therapy, the addition of dopamine agonists may increase the response rate to 60%.

Based on these data, the aim of this study was to evaluate the effects of combination therapy: dopamine agonists and somatostatin analogues on GH and IGF1 levels in patients with acromegaly being treated and monitored in the Endocrinology Clinic Cluj-Napoca.

Materials and methods

The study included 30 patients with active acromegaly, 21 women and 9 men, aged 29 to 74 years. The diagnosis of acromegaly was established on the basis of high serum GH levels, not suppressible below 1 ng/ml after oral glucose load, and high plasma IGF1 levels (over 300 ng/ml). All patients had prolactin levels over 20 ng/ml. Before entering the study 3 patients had undergone transsphenoidal surgery, 8 patients had received pituitary radiation therapy, 14 patients had undergone surgery and subsequently radiotherapy, and 5 patients had not received any treatment prior to initiating the combination therapy.

Patients were divided into 4 groups, according to IGF1, prolactin, basal GH levels and GH response to oral glucose load: group I, consisting of 4 patients, was treated with Octreotide 20 mg/month and Cabergoline 2 mg/week; group II, consisting of 15 patients, was treated with Octreotide 30 mg/month and Cabergoline 4 mg/week; group III: 3 patients, treated with Octeotide 30 mg/month and Bromocriptine 10 mg/day; group IV: 8 patients, treated with Lanreotide 30 mg/week and Cabergoline 2 mg/week. Follow-up was performed every 6 to 12 months after initiation of treatment by determining IGF1, prolactin and GH levels.

In assessing the effectiveness of combination therapy, we used an arbitrary scale for IGF1, PRL and GH values. A good therapeutic response was defined as IGF1 levels ≤300 ng/ml, PRL≤15 ng/ml, GH≤2 ng/ml, moderate response: IGF1 between 300-450 ng/ml, PRL 15-30 ng/ml, GH 2-5 ng/ml and poor response: IGF1>5 ng/ml, PRL>30 ng/ml and GH>5 ng/ml.

The RIA (radioimmunoassay) method was used for measuring IGF1. IGF1 levels vary by age and gender, values below 300 ng/ml being considered normal for all patients enrolled in the study. RIA was also used to determine PRL levels. The upper reference limit was 20 ng/ml for women and 15 ng/ml for men. RIA was used for GH measurements. For statistical analysis we used the Student t-test.

Results

In group I, IGF1 normalized after 6 months of treatment, with discrete increase after 12 months. PRL and GH levels steadily declined. After 12 months of treatment, IGF1 normalized in 50% of patients, PRL in 25% and GH in 100% of cases.

In group II, treated with Octreotide 30 mg/month and Cabergoline 4 mg/week, IGF1, PRL and GH levels slowly declined over 6 to 12 months. Although the Octreotide and Cabergoline dose was higher, we only observed good treatment response in 27% of cases for IGF1 levels, 20% for PRL and in over 50% for GH.

In group III, treated with Octreotide 30 mg/week and Bromocriptine 10 mg/day, IGF 1, PRL and GH levels gradually decreased, and IGF1 normalized in one third of patients after 12 months of treatment. In all patients, PRL and GH levels decreased by 50% following 12 months of treatment.

In the group treated with Lanreotide 30 mg/week and Cabergoline 2 mg/week, although GH levels fell below 2 ng/ml following OGTT after 6 months and below 1 ng/ml after 12 months of treatment, IGF1 and PRL normalized in only 25% of patients.

Analysis of IGF1 variation according to the type of medication and dose regimen shows the best response for Cabergoline 2 mg/week after the first 6 months of treatment. After 12 months, IGF1 levels were comparable, with a slight difference in favor of Cabergoline 4 mg/week (Figure 1).

Discussion

Dopamine agonists, Bromocriptine respectively, were the first pharmacological agents used for treating acromegaly [6]. The main goal of treatment is to achieve GH levels below 1 ng/ml after a glucose load and to normalize age and gender-matched IGF1 levels. Monotherapy with dopamine agonists achieves this goal in a limited number of cases [7]. As opposed to prolactinomas, much higher doses of Bromocriptine are required for adequate control of acromegaly, which increases the risk of side effects. Compared to Bromocriptine, Cabergoline has a longer half-

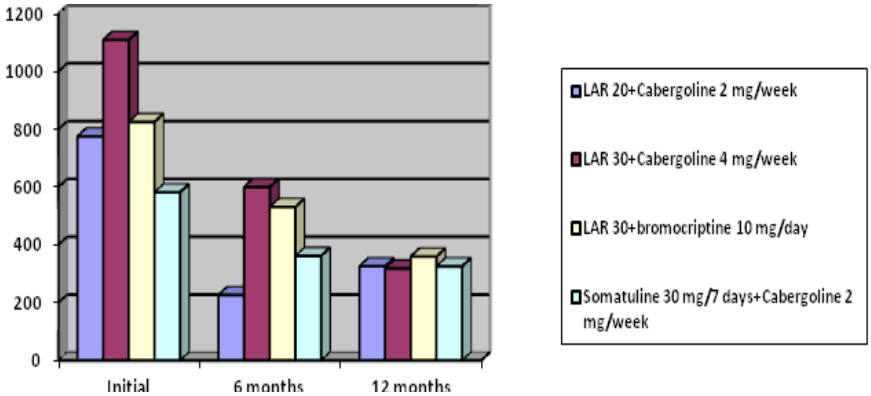

Figure 1. Analysis of IGF-1 variation according to the type of medication and dose regimen.

Table I. Treatment response according to IGF1, PRL and GH levels.

	IGF 1 ng/ml			PRL ng/ml			GH ng/ml		
	Good	Moderate	Poor	Good	Moderate	Poor	Good	Moderate	Poor
Group I n=4	2(50)	1(25)	1(25)	1(25)	3(75)	0	4(100)	0	0
Group II n=15	4(27)	6(40)	5(33)	3(20)	11(73)	1(7)	8(53)	6(40)	1(7)
Group III n=3	1(33)	1(33)	1(34)	0	3(100)	0	0	3(100)	0
Group IV n=8	2(25)	3(37.5)	3(37.5)	2(25)	6(75)	0	8(100)	0	0

life and greater binding affinity for dopamine D2 receptors, with increased clinical efficacy and reduced risk of side effects [8]. However, isolated Cabergoline use manages to cure the disease in a relatively small proportion of patients, ranging from 10 to 20%. Adding dopamine agonists to somatostatin analogue therapy substantially increases the response rate to 60% [9].

In our study, in group I (treated with Octreotide 20 mg/month and Cabergoline 2 mg/week) - with an initial mean IGF1 level of 775 ng/ml, PRL 55 ng/ml and GH 3916 ng/ml- IGF1 normalized in 50% of patients and PRL in 25% after 12 months of treatment.

In group II, although the Cabergoline dose was higher (4 mg/week), a good treatment response was achieved in 27% of cases for IGF1 and 20% for prolactin levels. A possible explanation could be higher baseline values for both IGF1 (mean=1109 ng/ml), PRL (mean=86 ng/ml) and GH (mean=9.01 ng/ml), prior to initiation of treatment.

As for the group treated with Bromocriptine 10 mg/day, IGF1 levels normalized in 33% of cases after 12 months of treatment. None of the patients responded well in terms of PRL and GH levels; one possible explanation (at least for PRL) could be that the ability to inhibit secretion is 34 times lower for Bromocriptine than Cabergoline [10].

Overall, good treatment response was achieved in 30% of cases for IGF1, 20% for PRL and 67% for GH levels. The majority of patients were classified as moderate responders according to both IGF-1 (37%), PRL (77%) and GH (30%).

Compared to similar studies [11] we report more modest results, although 25 out of 30 patients had previously undergone surgery (3/30) or radiotherapy (14/30), or both (5/30).

There are several clinical studies that report an inadequate response to dopamine agonist therapy. Colao et al. did not obtain biochemical remission for any of the 11 patients treated with 1-2 mg Cabergoline/week for 6 months [12], while Jackson et al. reported the normalization of IGF-1 and GH in 2 out of 10 patients with acromegaly treated with 0.5 mg Cabergoline/week [13].

Comparing the results in relation to the type of dopamine agonist used, a better response was obseved for Cabergoline (50% good response) than Bromocriptine (33% good response). These results are similar to those reported in a clinical study which included 11 patients with acromegaly treated with dopamine agonists [14].

Despite the limitations imposed by the small number of patients enrolled in our study, we can conclude that dopamine agonists represent a therapeutic alternative for patients with inadequate response to previous treatment, especially in the presence of hyperprolactinemia.

Conclusions

Combination therapy consisting of dopamine agonists and somatostatin analogues effectively reduces IGF1 levels in patients with mixed GH and PRL-secreting pituitary adenomas.

The decrease in IGF1 levels is directly correlated with the dose of Cabergoline used.

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