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Growth Hormone Levels in Patients with Active Acromegaly Treated with Somatostatin Analogues

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Abstract

Acromegaly is characterized by excessive growth hormone (GH) secretion and may result in high morbidity and mortality, particularly from cardiovascular disease. Normalized serum GH levels may abolish this untoward effect. Somatostatin analogues (SA) are usually prescribed following unsuccessful transsphenoid surgery for pituitary adenomas. The purpose of this analysis is to evaluate the effects of two SA, octreotide LAR and lanreotide SR, on GH levels in patients with active acromegaly. We reviewed the clinical data of patients with active acromegaly who were treated with SA for at least 12 months. The efficacy of octreotide LAR and lanreotide SR in lowering GH levels was retrospectively investigated. Sixteen patients with active acromegaly were enrolled in the analysis. Nine patients received octreotide LAR and 7 received lanreotide SR. The mean age when initiating SA therapy was 51 years, and the majority of patients were women and had macroadenomas. GH concentrations before and after SA treatment were 6.4 [1.8, 23.7] vs. 1.24 [0.3, 4.1] ng/ml (median [minimum, maximum], p=0.027) for the octreotide LAR group and 4.8 [1.4, 109] vs. 1.7 [0.3, 23.4] ng/ml (median [minimum, maximum], p=0.276) for the lanreotide SR group after a mean 44 months and 54 months of treatment, respectively. The rates of serum GH concentration below 2.5 ng/mL for octreotide LAR group and lanreotide SR group were 66.7% and 71.4%, respectively. In conclusion, octreotide LAR play a significant role in adjunctive therapy for active acromegaly, while GH levels declined significantly after a mean 44 months treatment. (J Intern Med Taiwan 2016; 27: 149-155)

Key Words: Acromegaly, Growth hormone, Somatostatin

Introduction

Acromegaly is characterized by excessive production of growth hormone (GH) and hence insulin-like growth factor-1 (IGF-1). Pituitary GH-secretion adenoma is the major cause of acromegaly.[1] Acromegaly is associated with increased morbidity and mortality, attributed primarily to cardiovascular and pulmonary comorbidities.[2] The mortality rate is related to GH levels, and normalizing serum IGF-1

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concentrations and decreasing basal GH levels to below 2.5 ng/mL or oral glucose tolerance test -derived GH levels below 2 ng/mL (radioimmunoassay method) can abolish this untoward effect.[3]

Therapy for acromegaly is targeted at remission of signs and symptoms, correcting local tumor compressive effects and reducing GH and IGF-I levels to normal values.[4]Transsphenoid surgery (TSS) is the first therapeutic opinion for GH-secreting pituitary adenomas. The successful rate of TSS is higher than 80% in microadenoma, but less than 50% in macroadenoma. Rapid reduction of GH levels, low incidence of postoperative hypopituitarism, and low surgical mortality rates may be expected with an experienced neurosurgeon. If surgery fails to decrease GH/IGF-1 levels, or is impossible or contraindicated, medical therapy with/without radiotherapy is mandatory.[2]

Somatostatin analogues (SA), dopamine agonists and GH receptor antagonists are currently available drugs for treatment of acromegaly. Somatostatin analogues are the mainstay of medical therapy for persistent or recurrent acromegaly following unsuccessful TSS in Taiwan, despite increasingly used as primary therapy.[5] Most experts have stated that SA are indicated at least sometime during the management of acromegaly patients.[6] The efficacy of SA in therapy for acromegaly varies among the different formulations. Previous studies showed that octreotide LAR had greater efficacy in achieving GH normalization than lanreotide SR among subjects with acromegaly.[7,8] The purpose of this analysis is to evaluate the effects of the two SA, octreotide LAR and lanreotide SR, in decreasing GH in patients with active acromegaly in a medical center of north Taiwan.

Materials and Methods

We reviewed the patients with active acromegaly who were treated with either octreotide LAR or lanreotide SR for at least 12 months from January 1, 2000 to April 30, 2008 in a medical center of north Taiwan. The efficacy of octreotide LAR and lanreotide SR in lowering GH levels was retrospectively investigated.

Sixteen patients with a clinical diagnosis of acromegaly who were treated with octreotide LAR 30 mg intramuscularly (i.m.) every 4 weeks or lanreotide SR 30 mg i.m. every 2 weeks were enrolled in the analysis. Blood samples were obtained on the day before SA injection and GH was measured by radioimmunoassay. Serum IGF-I was measured by a chemiluminescence immunoassay. The therapeutic goal was based on the mortality reduction, with a random GH levels below 2.5 ng/mL.[9] Hypertension was defined as a history of prescription of antihypertensive drugs, or persistently raised blood pressure above 140/90 mmHg.

Data are expressed as mean ± standard deviation, median [minimum, maximum], or number with percentage. The Pearson chi-square test was used for comparison of categorical data. A paired t test was used to compare GH levels at baseline, 1 year after SA treatment, and at the end of follow-up. Pearson product moment correlation was employed to assess the relationships between hormonal decline and baseline levels and length of follow-up for GH. Cox regression was used to evaluate the predictive factors for a GH < 2.5 ng/mL. All tests were two-tailed, and a p value less than 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS Chinese version for Windows, 12.0). The authors have no conflicts of interest to disclose. There were no sources of funding that could have influenced the outcome of this work.

Results

Characteristics of the patients at baseline

Nine patients received octreotide LAR and 7 received lanreotide SR. Three of the 7 patients

who received lanreotide SR were shifted to octreotide LAR without a washout period 31, 33 and 36 months later. Three patients in our analysis with GH levels less than 2.5 ng/ml but higher than 1.0 ng/mL received SA as secondary treatment. The baseline characteristics of the population are summarized in Table 1. The majority of the patients had pituitary macroadenomas, and women predominanted. The mean age when initiating SA therapy was 51 years, and the mean duration of pharmacologic therapy was 48 months. Most of the patients except 2 were treated with SA as secondary therapy. Five of the patients (55.6%) in the octreotide LAR group had been previously treated by TSS once alone, and 3 patients (33.3%) by TSS once followed by radiotherapy. In the lanreotide SR group, 4 patients (57.1%) had been previously treated with TSS once alone, and 2 patients (28.6%) with TSS once followed by radiotherapy.

Changes in growth hormone levels after the 1-year follow-up

Two patients in the lanreotide SR group and 1 patient in the octreotide LAR group had GH levels below 2.5 ng/ml (1.49, 1.41, and 1.78 ng/mL) at baseline. The pre-operative and 1-month post-operative GH concentrations for the octreotide LAR and lanreotide SR groups were 18.3 [5.5, 71.5] vs. 6.2 [1.7, 10.9] (p=0.090) and 19.3 [14.0, 362.0] vs. 15.9 [6.9, 260.7] ng/mL (p=0.403), respectively. The GH concentrations before and 1 year after SA treatment in the respective groups were 6.4 [1.8, 23.7] vs. 2.1 [0.6, 13.5] (p=0.045) and 4.8 [1.4, 109.0] vs. 3.4 [1.27, 107.0] (p=0.609) ng/mL, respectively. At the end of follow-up, the GH concentrations post-drug treatment were still significantly lower than those of pre-treatment concentrations in the octreotide LAR group (1.2 [0.3, 4.2] vs. 6.4 [1.8, 23.7], p=0.027), but not in the lanreotide SR group (1.7 [0.3, 23.4]vs. 4.8 [1.4, 109.0], p=0.276) (Table 2).

The change of GH and IGF-1 during follow-up period were illustrated in figure 1. The decline of serum GH was 3.6 ng/mL and 3.7 ng/mL at 1-year therapy and end of follow- up, respectively. At the end of follow-up, serum GH levels were less than 2.5 ng/mL in 6 patients (66.7%) in the octreotide LAR group, and 5 (71.4%) in the lanreotide SR group. The change in GH concentrations were -3.9 [-20.9, -0.5] ng/mL in the octreotide LAR group and -3.5 [-85.6, 0.79] ng/mL in the lanreotide SR group.

IGF-1 was evaluated in most but not all individuals during follow up period Three of the 10 patients analysed for IGF-1 had normalization with age and sex matched 1 year after SA treatment. Normalized IGF-1 was achieved in 4 of 13 patients at the end of treatment.

The GH concentrations before and 1 year after SA treatment in the 3 patients receiving lanreotide SR initially then shifting to octreotide LA were 6.4 [4.8, 109.0] vs. 3.6 [1.3, 107.0] ng/mL, respectively.

Table 1. Characteristics of the patients

	Octreotide LAR (n=9)	Lanreotide SR (n=7)	All (n=16)
Age (years)	48 ± 17	55 ± 21	51 ± 18
Male (n , %)	2 (22.2)	2 (28.6)	4 (25.0)
Weight (kg)	69.5 ± 10.3	65.4 ± 12.4	67.5 ± 11.2
Macroadenoma (n, %)	8 (88.9)	4 (57.1)	12 (75.0)
Pituitary surgery (n, %)	8 (88.9)	6 (85.7)	14 (87.5)
Radiotherapy (n, %)	3 (33.3)	2 (28.6)	5 (31.3)
Mean time since diagnosis (month)	135 ± 98	73 ± 61	106 ± 86
Length of SA therapy (month)	44 ± 30	54 ± 26	48 ± 28
Type 2 diabetes (n, %)	3 (33.3)	2 (28.6)	5 (31.3)
Hypertension (n, %)	0 (0.0)	3 (42.9)	3 (18.8)

Data are expressed as n (%), mean ± standard deviation.

Table 2. GH levels at follow-up

GH level (ng/mL)	Octreotide LAR (n=9)	Lanreotide SR (n=7)	All (n=16)
Pre-operation (ng/mL)*	18.3 [5.5, 71.5]	19.3 [14.0, 362.0]	18.8 [5.5, 362.0]
Post-operation (ng/mL)*	6.2 [1.7, 10.9]	15.9 [6.9, 260.7]	9.6 [1,7, 260.7]
Pre-SA, baseline (ng/mL)*	6.4 [1.8, 23.7]	4.8 [1.4, 109.0]	5.4 [1.4, 109.0]
Post-SA, 1year-therapy (ng/mL)*	2.1 [0.6, 13.5]†	3.4 [1.3, 107.0]	2.1 [0.6, 107.0]†
Changes, 1 year-therapy (ng/mL)*	-3.6 [-10.1, 4.3]	-2.0 [-5.2, 7.8]	-2.3 [-10.1, 7.8]
Decrease, 1 year-therapy (%)*	-65.2 [-88.6, 169.5]	-1.8 [-80.3, 551.8]	[-88.6, 551.8]
GH<2.5, 1 year-therapy (n, %)	6 (66.7)	3 (42.9)	9 (56.3)
End of follow-up (ng/mL)*	1.2 [0.3, 4.2]††	1.7 [0.3, 23.4]	1.4 [0.3, 23.4]
Change, end of follow-up (ng/mL)*	-3.9 [-20.9, -0.5]	-3.5 [-85.6, 0.8]	-3.7 [-85.6, 0.8]
Decrease, end of follow-up (%)*	-44.9 [-92.1, -30.3]	-72.5 [-95.7, 56.0]	-75.2 [-95.7, 56.0]
GH<2.5, end of follow-up (n, %)	6 (66.7)	5 (71.4)	11 (68.8)
GH<2.5 plus normalized IGF-1 (n, %)	2 (22.2)	3 (42.9)	5 (31.3)

*data presented as median [min, max].
†significant difference between pre-SA therapy and 1-year therapy (p=0.045 in octreotide LAR group, p=0.047 in all patients), paired t test.
††significant difference between pre-SA therapy and end of follow-up (p=0.027), paired t test.
GH: growth hormone; SA: somatostatin analogue.

At the end of follow-up after shifting to octreotide LAR, the GH concentrations post-drug treatment were 1.4 [1.2, 8.0] ng/mL. Two of 3 patients achieved therapeutic targets of GH below 2.5 mg/dL.

Three patients in octreotide LAR group and no patients in lanreotide SR group were basal GH less than 1 ng/mL 1 year after SA therapy. Three patients in octreotide LAR group and 1 in lanreotide SR group were basal GH less than 1 ng/mL at end of follow up.

Correlation of changes in growth hormone levels and clinical characteristics

In the octreotide LAR group, GH levels at the 1-year follow-up were directly correlated with GH levels at baseline (r =0.727 and *P*=0.027). Hormonal decline for GH at the end of follow-up was positively correlated with baseline GH levels (r = 0.986 and *P*<0.001), and patients with higher baseline GH levels had a greater GH declines. Growth hormone decline was not related to length of treatment.

Predictive factors of GH < 2.5 ng/ml

Age, gender, microadenoma, surgery, radiotherapy, and GH levels at baseline and 1-yr follow up were not predictors of GH < 2.5ng/mL on Cox regression analysis. (Table 3)

Discussion

Criteria of cure of acromegaly by the consensus in 2000 were circulating IGF-I is reduced to an sex and age-adjusted normal range and nadir GH levels is less than 1 ng/mL after an oral glucose load.[10] Using ultrasensitive assays, criteria of cure of acromegaly by the consensus in 2010 were normalized IGF-1 levels and random GH < 1 ng/mL or nadir GH < 0.4 ng/mL after an oral glucose loading.[11] It's reasonable that 3 patients in our analysis with GH levels less than 2.5 ng/ml but higher than 1.0 ng/mL received SA as secondary treatment. IGF-1 was evaluated in most but not all individuals during follow up period. Measurement of IGF-1 is recommended for biochemical diagnosis of acromegaly.[12] To evaluate the effectiveness of medical treatment, serum IGF-1 and GH should be measured after 12weeks just prior to the next dose of SA.[12]

Although substantial clinical data have been published on the use of SA for treatment of

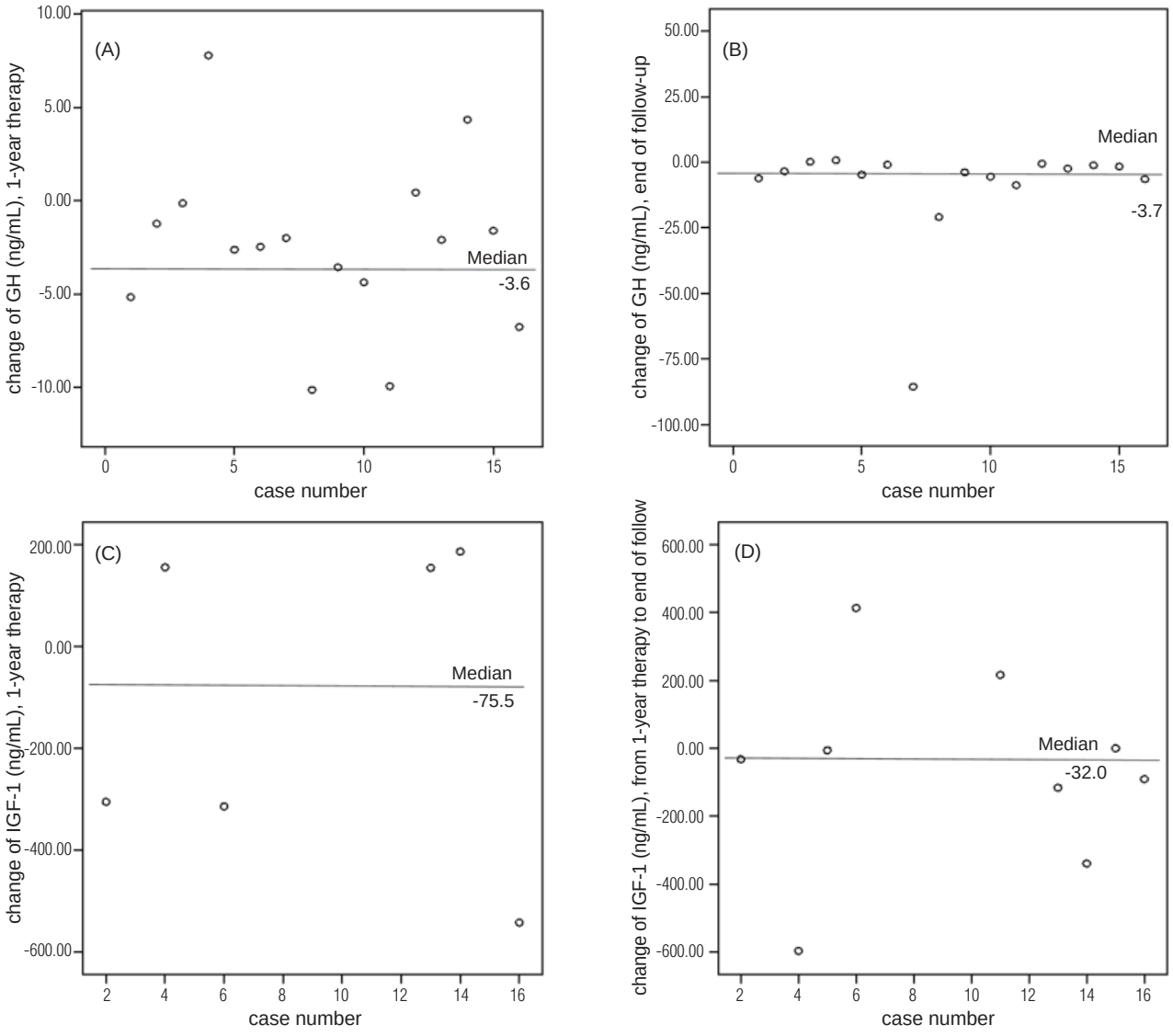

Figure 1. A: change of growth hormone after 1-year therapy. B: change of growth hormone at end of follow-up. C: Change of insulin-like growth factor-1 at 1-year therapy (n=5). D: change of insulin-like growth factor-1 from 1-year therapy to end of follow up (n=9). GH: growth hormone; IGF-1: insulin-like growth factor-1.

Table 3. The hazards ratio of various uni-variate on achieving GH< 2.5 ng/mL at end of follow up

	Unadjusted		
	Hazard ratio	95% CI	p
Octreotide LAR	0.867	0.260-2.896	0.867
Age	1.010	0.979-1.042	0.523
Male sex	0.795	0.164-3.858	0.776
Macroadenoma	1.254	0.326-4.817	0.742
Surgery	2.342	0.277-19.792	0.435
Radiotherapy	3.333	0.557-19.949	0.187
GH levels at baseline	0.965	0.753-1.237	0.778
GH levels at 1 year follow-up	0.794	0.545-1.157	0.230

acromegaly, the efficacy varies from study to study. In this retrospective analysis of acromegalic patients mainly affected by macroadenoma, treatment with SA was effective in reducing GH to less than 2.5 ng/mL. The therapeutic goal for GH was achieved in 66.7% of patients in the octreotide LAR group and 42.9% in the lanreotide group after12 months. These figures are compatible with those in previous reports.[7] GH level significantly declined after 1 year of therapy and a mean 44 months of treatment in the octreotide LAR group. Therefore, drug efficacy maintained with the length of treatment in the octreotide LAR group. This result was consisted with the report of Cozzi et al on 9 years sustained treatment with octreotide LAR.[12] The cases numbers in our analysis were too small to compare the rate of achieving GH < 2.5 ng/mL between the two groups. Data from a previous meta-analysis showed octreotide LAR remains more efficacious than lanreotide SR, even when potential preselection effects for SA responsiveness are removed.[7]

Our data showed that the pretherapy GH level was not a predictor for meeting biochemical criteria for control with SA therapy. Also, the pre-SA therapy GH levels in both groups were identical. Thus, the difference in efficacy between octreotide LAR and lanreotide SR could not be explained by differences in baseline GH levels. However, our results should be interpreted carefully, since our case number was small. Furthermore, patient selection bias should also be considered. The relationship between pretherapy GH levels and achieving the therapeutic goal was controversial. The metaanalysis showed that the likelihood of achieving therapeutic hormonal targets is greater in patients with lower baseline GH levels.[7] However, the report by Cozzi et al. showed that patients with initially higher basal GH values achieved hormonal targets as often as patients with baseline lower levels after up to nine-years of follow up.[13]

There were 3 main limitations to this study. Firstly, the sample size was too small to compare the efficacy between octreotide LAR and lanreotide SR therapy. This is probably a consequence of the rarity of acromegaly. Secondary, patients and drugs selection bias should be considered, since the decision making was dependent on the expertise of the endocrinologists. Thirdly, the therapeutic dose was not titrated in our groups. The octerotide LAR dose included 10 mg in 18%, 20 mg in 48%, 30 mg in 29% and 40 mg in 4.8% of patients, and the lanreotide SR dose was 30 mg in 75.3% and 60 mg in 24.6% of patients included in the meta-analysis.[7] Furthermore, lanreotide injection monthly was approval in 2007, while lanreotide SR every 2 weeks is not in clinical use now.

Our retrospective analysis showed octreotide LAR may play a significant role in the adjunctive therapy of active acromegaly. A well-designed prospective head-to-head comparison study is mandatory to clarify the efficacy for biochemical control between octreotide LAR and lanreotide SR therapy.

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以體抑素類似物治療肢端肥大症病患後之生長激素變化

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摘　要

肢端肥大症是因為生長激素分泌過多所引起，並且會引發心血管疾病等併發症，而治療至正常範圍的生長激素濃度後可減少併發症與死亡率。腦下垂體腫瘤切除手術後，常投與體抑素類似物。本文的目的為評估兩種不同的體抑素類似物，即 octreotide LAR 與 lanreotide SR 的療效。我們回顧性分析接受 octreotide LAR 或 lanreotide SR 治療至少 12 個月的肢端肥大症病患的臨床資料，評估兩種不同的藥物降低生長激素的效果。本分析包括 16 位病患，其中 9 位接受 octreotide LAR 治療，7 位接受 lanreotide SR 治療。開始接受體抑素類似物治療的平均年齡為 51 歲，大多數病患為女性與大的腦下垂體腫瘤。接受 octreotide LAR 平均用藥物治療 44 個月與 lanreotide SR 平均用藥物治療 54 個月治療前後的生長激素濃度分別為 6.4 [1.8, 23.7] vs 1.24 [0.3, 4.1] (中位數 [最小值，最大值]，p=0.027) 及 4.8 [1.4, 109] vs 1.7 [0.3, 23.4] ng/ml (中位數 [最小值，最大值]，p=0.276)。接受 octreotide LAR 或 lanreotide SR 治療之生長激素達到低於 2.5 ng/mL 的比率分別為 66.7% vs 71.4%。體抑素類似物 octreotide LAR 在肢端肥大症的治療上扮演重要角色，平均治療 44 個月後，生長激素的濃度有顯著的下降。