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Investigation into the Efficacy and Safety of Octreotide LAR in Japanese Patients with Acromegaly: Shizuoka Study

YUTAKA OKI*, TATSUHIDE INOUE**, MITSUO IMURA***, TOKUTARO TANAKA#, RIEKO GENMA##, MASAYASU IWABUCHI###, YUJI HATAYA†, YUJI MATSUZAWA††, KAZUMI IINO*, SHIGERU NISHIZAWA††† AND HIROTOSHI NAKAMURA*

* *Second Division, Department of Medicine, Hamamatsu University School of Medicine, 1-20-1 Handayama Higashi-ku, Hamamatsu 431-3192, Japan*
** *Diabetes and Endocrinology Center, Shizuoka General Hospital, 4-27-1 Kitaando Aoi-ku, Shizuoka 420-8527, Japan*
*** *Department of Endocrinology and Metabolism, Yaizu City Hospital, 1000 Michihara, Yaizu, Shizuoka 425-8505, Japan*
# *Department of Neurosurgery, Seirei Hamamatsu General Hospital, 2-12-12 Sumiyoshi Naka-ku, Hamamatsu 430-8558, Japan*
Division of Endocrinology, Department of Internal Medicine, Seirei Hamamatsu General Hospital, 2-12-12 Sumiyoshi Naka-ku, Hamamatsu 430-8558, Japan
Department of Endocrinology and Metabolism, Seirei Mikatahara General Hospital, 3453 Mikatagahara-cho Kita-ku, Hamamatsu 433-8558, Japan
† *Department of Endocrinology and Metabolism, Shizuoka Hospital, 10-93 Ote-cho, Aoi-ku, Shizuoka 420-8630, Japan*
†† *Department of Neurosurgery, Seirei Numazu Hospital, 902-6 Shichitanda, Matsushita Hon-aza, Numazu, Shizuoka 410-8555, Japan*
††† *Department of Neurosurgery, University of Occupational and Environmental Health, Kitakyushu, Fukuoka 807-8555, Japan*

Abstract. The efficacy and safety of the long-acting repeatable formulation of octreotide (OCT-LAR) treatment in patients suffering from acromegaly was investigated retrospectively in Shizuoka prefecture, Japan. Thirty patients (11 male, 19 female; average age, 48.9 years old), 29 of whom had undergone transsphenoidal surgery previously, were treated with OCT-LAR. OCT-LAR was injected i.m. every 4 weeks with an intended protocol of 20 mg over 24 months, however, 46.7% of patients required the dose of OCT-LAR to be increased. The final average dose of OCT-LAR was 25.0 ± 6.8 mg. Administering OCT-LAR significantly decreased serum GH and insulin-like growth factor 1 (IGF-1) levels (from 13.7 ± 11.9 to 5.8 ± 7.3 μg/L and from 585 ± 263 to 339 ± 193.7 μg/L after 3 months, respectively). Among patients treated with OCT-LAR, 56.7% expressed ≤2.5 μg/L serum GH and 53.3% displayed serum IGF-1 levels within the normal range, while 36.7% met both criteria that indicated treatment success. A sufficient outcome was achieved in 73.3% of patients when the rate of GH ≤2.5 μg/L or normalization of IGF-1 was accumulated. OCT-LAR did not have a negative effect on glucose tolerance when hemoglobin A1c was used as a marker. A gallbladder polyp was found only in 1 patient but it was uncertain whether OCT-LAR was involved in its development because the patient was not examined before OCT-LAR treatment. There were no abnormalities on liver function tests in any patients. In conclusion, our results showed that OCT-LAR was safe and effective as a therapeutic option for Japanese patients with acromegaly in a postoperative setting, by controlling the disease activity.

Key words: Octreotide, Acromegaly, GH, Insulin-like growth factor 1

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THE MAJORITY of patients with acromegaly suffer from pituitary adenoma, from which excessive secretion of GH induces a high incidence of pathological complications including maladaptive changes in the face and limbs, as well as diabetes mellitus, hypertension, hyperlipidemia, arteriosclerosis, and cardiovascular disorders [1]. According to a previous report, acromegaly increased the rate of mortality, while the cumulative survival rate of untreated patients was <40% over the last 20 years [2]. Observing the relationship between GH level and mortality, the 50% survival rate in three groups with GH levels of >5 μg/

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Correspondence to: Yutaka OKI, Second Division, Department of Medicine, Hamamatsu University School of Medicine, 1-20-1 Handayama Higashi-ku, Hamamatsu 431-3192, Japan.
E-mail: okitaka@hama-med.ac.jp

L, <5 μg/L, and <2 μg/L were reported to be approximately 2, 19 and 25 years, respectively [2]. Thus, the current objective in the treatment of acromegaly is to prevent the underlying pathogenic complications induced by excessive GH secretion.

In Japan, the diagnosis and treatment of acromegaly is currently performed based upon the "Guideline for Diagnosis and Treatment of Acromegaly 2007", with surgery, medical therapy and radiotherapy listed as the treatments. Surgery, usually transsphenoidal surgery (TSS), is the predominant choice of initial therapy, however, somatostatin analogs, dopamine agonists, or a GH receptor antagonist is also available for medical therapy.

The long-acting repeatable (LAR) formulation was developed to enable long-term treatment with octreotide acetate (OCT). According to previous reports, the percentage of patients with acromegaly achieving GH ≤2.5 μg/L was 44–68%, and the efficacy rate of patients with normal IGF-1 levels was 34–70%, while the rate of patients with tumor shrinkage ranged between 72 and 88% after OCT-LAR treatment [3, 4].

However, few studies have investigated a large number of Japanese acromegaly patients treated with OCT-LAR. Therefore, we retrospectively investigated 30 Japanese patients with acromegaly in order to determine the efficacy and safety of OCT-LAR treatment.

Materials and Methods

Subjects and methods

The subjects enrolled in the current study had a definite diagnosis of acromegaly or pituitary gigantism based on the "Guideline for Diagnosis and Treatment, 2006". A total of 30 patients (11 men and 19 women; mean age, 48.9 years, age range, 19–75 years, at the beginning of OCT-LAR treatment) were analyzed retrospectively. All but 1 patient had undergone TSS prior to treatment with OCT-LAR. One patient received OCT-LAR treatment without TSS because she had to continue warfarin after Bentall surgery. Twelve patients were treated with TSS alone before OCT-LAR treatment. Radiosurgery was performed at least 3 years before OCT-LAR treatment. Fifteen patients had been treated with bromocriptine (2.5–20 mg/day) before starting OCT-LAR. One patient continued cabergoline (0.5 mg/week, p.o.) before and during OCT-LAR treatment. The details of previous treatment are summarized in Table 1. Four patients with diabetes mellitus were treated with sulfonylurea (*n*=1), nateglinide (*n*=1) or insulin (*n*=2). Other than adjusting the dose of OCT-LAR, the patient's course of treatment was not altered during this study. The study was approved by the ethics committee of all participating hospitals and written consent regarding the use of data was obtained from all patients, in accordance with international guidelines for informed consent in clinical research.

Table 1. The previous treatments of patients with acromegaly in this study

previous treatment	*n*
none	1
TSS alone	12
TSS + bromocriptine	10
TSS + cabergoline	1
TSS + RS	1
TSS + RS + bromocriptine	5
total	30

TSS; transsphenoidal surgery, RS; radiosurgery

Treatment with OCT-LAR was started at 20 mg, injected i.m. into the hip every 4 weeks for 24 months, after introducing OCT 200–300 μg s.c. for 2 weeks. The changes in serum GH and IGF-1 concentrations over this time course were determined. To investigate the side effects of OCT-LAR treatment, liver function tests as well as hemoglobin A1c (HbA1c) levels were monitored every 3 months, combined with abdominal imaging tests (abdominal computed tomography or echography) performed every 12 months.

For a single octreotide test, each patient was injected s.c. with 100 μg octreotide, and blood samples were collected before and every hour after drug administration for up to 6 h. The percentage decrease in serum GH concentration was calculated using nadir GH after the single s.c. injection of octreotide or OCT-LAR treatment.

Serum GH and IGF-1 concentrations were determined by immunoradiometric assays (GH Kit Dai-ichi and IGF-1 IRMA Dai-ichi; TFB Inc., Japan, respectively).

Assessment of biochemical response

Serum GH and IGF-1 were analyzed and determined at the clinical laboratories of each hospital. The biochemical results were categorized as follows: (1) success was achieved when serum GH was ≤2.5

μg/L and IGF-1 was within the Japanese age/gender-matched normal range; and (2) partial success was considered when only serum GH (≤2.5 μg/L) or IGF-1 (within the Japanese age/gender-matched normal range) was observed.

Statistical analysis

Changes in GH, IGF-1 and HbA1c levels over the time course were analyzed using one-way ANOVA with Dunnett's analysis performed post hoc. Values are expressed as mean ± SD, and $P<0.05$ was considered statistically significant. All calculations were performed using Prism v. 4.0 (GraphPad Software Inc., San Diego, CA USA).

Results

Dose and duration of OCT-LAR treatment in this study

Twenty-six patients (87%) were treated for 24 months, 3 patients for 18 months, and 1 patient for 12 months. The final doses of OCT-LAR injected by the end of the study were 10, 20, 30 and 40 mg, which were administered to 1, 15, 12 and 2 patients, respectively (mean dose 25.0 ± 6.8 mg).

Effects of OCT-LAR on serum GH and IGF-1 levels

Serum GH levels were reduced significantly to 5.8 ± 7.3 μg/L after 3 months of OCT-LAR treatment compared with original baseline GH levels of 13.7 ± 11.9 μg/L (Fig. 1A). The reduction in GH levels was maintained for up to 24 months provided the OCT-LAR treatment continued (Fig. 1A). Serum IGF-1 levels were reduced significantly from 585 ± 263.0 μg/L (baseline) to 339 ± 193.7 μg/L after 3 months of OCT-LAR treatment. Again, patients maintained the reduced IGF-1 levels for up to 24 months, provided the OCT-LAR treatment continued (Fig. 1B).

Success rate of controlling serum IGF-1 and GH concentrations in patients treated with OCT-LAR

The age/gender-matched normal range of serum IGF-1 for each patient was calculated based upon the reference values proposed by Shimatsu *et al*. in 2007 [5]. We found OCT-LAR treatment returned IGF-1 levels to within the age/gender-matched normal range in 53.3% (16/30) of patients, when each patient's IGF-1 level was at its minimum (Fig. 2B). A further 7 patients showed that serum IGF-1 levels were reduced by ≥50% when compared with baseline, however their IGF-1 concentrations were not within the normal range (Table 2).

A serum GH concentration of ≤2.5 μg/L was considered as the cut-off concentration at which the disease was controlled by drug therapy. Based on this GH cut-off value, as well as normalized IGF-1 concentration, OCT-LAR successfully controlled the disease in 36.7% (11/30) of patients (Table 3). In patients achieving only GH concentration of ≤2.5 μg/L or IGF-1 normalization, OCT-LAR treatment was con-

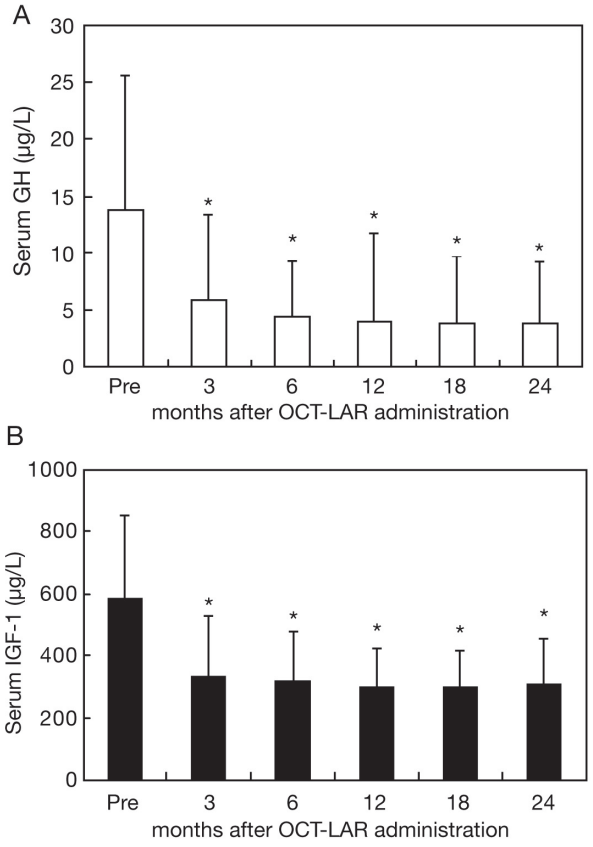

Fig. 1. Changes in serum GH and IGF-1 concentrations after administration of OCT-LAR in patients with acromegaly. Each column represents the mean serum GH (panel A) and serum IGF-1 (panel B) levels and brackets indicate the SD. Statistical analysis was performed using one-way ANOVA followed by Dunnett's test. *, $P<0.001$ *vs*. serum GH and IGF-1 levels immediately prior to administration of OCT-LAR.

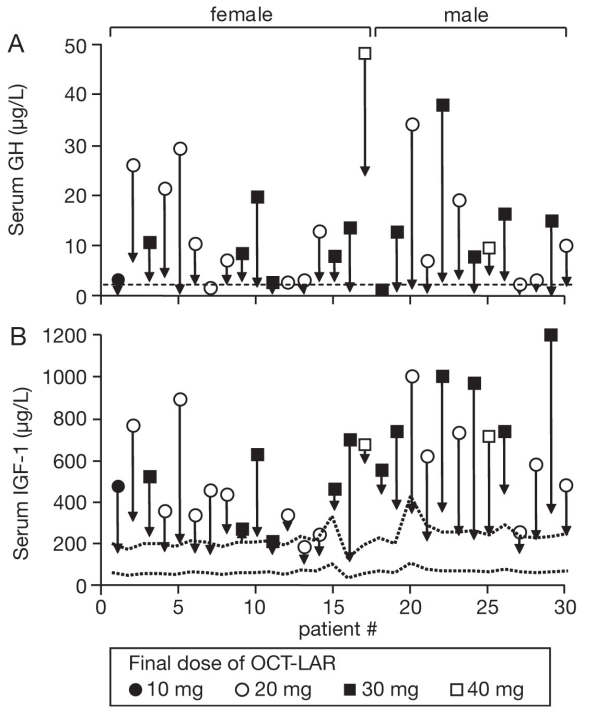

Fig. 2. Changes in serum GH and IGF-1 concentrations in each patient with acromegaly after administration of OCT-LAR.
Each arrow indicates the change in GH (panel A) and IGF-1 (panel B) levels. Broken line in panel A indicates the serum GH level of 2.5 μg/L. Broken lines in panel B indicate the reference range of IGF-1 adjusted for age/gender.

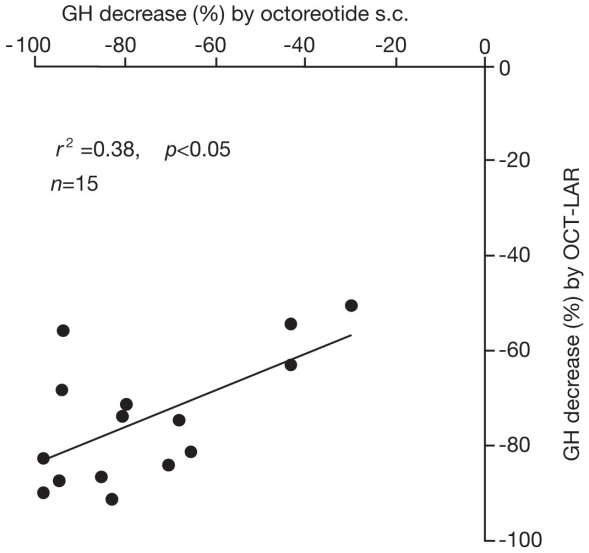

Fig. 3. Correlation between GH decrease (%) after a single s.c. injection of OCT and that during OCT-LAR treatment in patients with acromegaly.

Table 2. IGF-I reduction and normalization rate by OCT-LAR treatment in patients with acromegaly

n=30	≥ 50% reduction	< 50% reduction
Normalization	12 (40.0%)	4 (13.3%)
Non-normalization	7 (23.3%)	7 (23.3%)

Table. 3 Success rate of OCT-LAR treatment in patients with acromegaly

Assessment	n	%
Success		
GH≤2.5 μg/L and normal IGF-1	11 (2)	36.7
Partial success		
GH≤2.5 μg/L and IGF-1 above normal	6 (4)	20
GH>2.5 μg/L and normal IGF-1	5 (2)	16.7
subtotal	11 (6)	36.7
Failure		
GH>2.5 μg/L and IGF-1 above normal	8 (6)	26.7
total	30 (14)	100

The numeral in the parenthesis represents the number of patients who were increased the dose of OCT-LAR.

sidered a partial success (Table 3). The rate of success plus partial success was 73.3% (22/30). In 14 patients, for whom the dose of OCT-LAR was increased from 20 to 30 mg, the success rate was increased from 0% to 7.1% (1/14) and the partial success rate was increased from 14.3% (2/14) to 35.7% (5/14). In 2 patients, the dose of OCT-LAR was increased further from 30 to 40 mg. There were no additional effects on GH or IGF-1.

It was also investigated whether it was possible to predict the therapeutic effect of OCT-LAR by analyzing the rate at which GH concentration was reduced following a single s.c. injection of OCT. A weak but significant correlation was observed between GH reduction (%) after a single s.c. injection of OCT and that during OCT-LAR treatment (r^2=0.38, P<0.05; Fig. 3).

Adverse events

OCT-LAR treatment did not influence HbA1c levels (from an initial 6.05 ± 1.20% to 5.82 ± 0.88% after 24 months, P>0.05). This suggests that OCT-LAR treatment had a negligible effect on glucose tolerance (Fig. 4). A gallbladder polyp was observed in

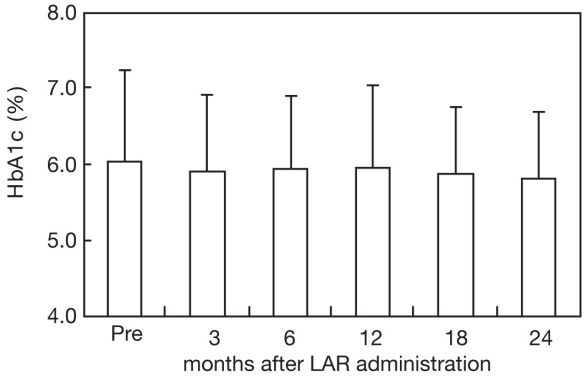

Fig. 4. Changes in HbA1c levels after administration of OCT-LAR in patients with acromegaly.
Each column represents mean HbA1c levels and brackets indicate the SD. There were no significant changes in HbA1c during OCT-LAR treatment. Statistical analysis was performed using one-way ANOVA.

1 patient 12 months after the introduction of OCT-LAR, however, this patient had not undergone imaging tests for abdominal complications before that time. Therefore, it is uncertain whether gallbladder polyp was caused by OCT-LAR. No patients showed elevated liver function that exceeded their normal levels by 2.5-fold (Table 4).

Table 4. Biochemical results during OCT-LAR treatment in patients with acromegaly

		normal range	Pre	Post
AST	IU/L	10 40	17.6 ± 6.4	18.9 ± 5.7
ALT	IU/L	5 - 40	19.6 ± 13.2	18.4 ± 9.7
Al-P	IU/L	115 - 359	214.3 ± 64.3	191.5 ± 60.1
γ-GTP	IU/L	Male <70 Female <30	24.0 ± 18.7	22.0 ± 11.0

Discussion

Acromegaly is a rare disease that affects an estimated 4–7 per million persons every year [6] but its prevalence may be higher [7, 8]. The mortality rate for patients with acromegaly is high, even when treated by surgical intervention [9]. The primary treatment for acromegaly is surgical removal of the pituitary tumor, with drug therapy also employed when total removal of the tumor is not achieved because of its localization or size [1, 10]. Drug and additional therapeutic options include somatostatin analogs [3], dopaminergic agents [11], GH receptor antagonist that is capable of inhibiting the action of GH in the liver [12], and radiosurgery [13]. Recently, OCT-LAR has been tried as an initial therapy in treating acromegaly, administered alone as the principal therapy or in conjunction with surgery [14, 15]. In Japan, OCT-LAR is a relatively new therapeutic option and few studies have reported its therapeutic effects in Japanese patients. Therefore, in this study, we investigated the therapeutic and adverse effects of OCT-LAR, using a relatively large sample of Japanese patients with acromegaly.

For the treatment of acromegaly, it is essential to lower the serum concentrations of GH and IGF-1, as well as reduce the physical stress from the pituitary tumor [2, 16]. We found that serum levels of GH and IGF-1 were significantly lowered by administering OCT-LAR, and this attenuation in serum levels was maintained throughout the 24-month study period, provided OCT-LAR treatment was continued. Although serum IGF-1 concentration was normalized in 53.3% of patients, we found that the success rate, which met GH ≤2.5 μg/L and normal IGF-1, was 36.7%. However, 73.3% of patients were judged a success or partial success, which was consistent with a previous study [17].

The success rate calculated may seem relatively low, however, the dose of OCT-LAR was only increased in 14 patients (48.3%). Only 1 patient exhibited a treatment-related adverse event (biliary calculus/gallbladder polyp) during the treatment with OCT-LAR, and the elevation in dose may have been responsible for this. A higher success rate in lowering GH and IGF-1 levels might have been achieved if the dose of OCT-LAR had been increased, as previous studies have reported that concentrations of GH and IGF-1 are decreased in response to increasing the OCT-LAR dose to 30 mg or 40 mg, when the secretion of GH and IGF-1 is not sufficiently suppressed with 20 mg [15, 18]. To obtain the true therapeutic effects of OCT-LAR, the expression of the somatostatin receptor subtypes 2 or 5 in the GH-producing pituitary adenoma is required [19]. A weak correlation was evident between the reduction in GH concentration in response to OCT-LAR and that by s.c. injection of OCT at an early stage, which enables prediction of the therapeutic effect of OCT-LAR.

Diabetes mellitus is associated strongly with acromegaly, and it has been reported recently that changes in blood glucose levels in patients treated with OCT for 6 months are not significantly different from those

in patients treated with surgery [20]. We investigated whether OCT-LAR influenced glucose tolerance, using the changes in HbA1c as an index. Overall, HbA1c was not elevated in patients treated with OCT-LAR until 24 months after initial administration. The somatostatin analogue may have little influence in glucose tolerance because of its inhibitory effect on insulin secretion [21]. The balance of improving insulin sensitivity by lowering GH and decreasing insulin secretion in response to a somatostatin analogue has been suggested to influence glucose tolerance in patients with acromegaly [22]. However, another study has reported that the treatment with octreotide for 2–3 weeks did not alter the response to the 75 g oral glucose tolerance test in Japanese patients with acromegaly [23]. Changes in ring size before and after administration of OCT-LAR were investigated in 7 patients; all of whom displayed reduced ring sizes (data not shown).

Our results provided novel insight into the efficacy and safety of OCT-LAR, but the retrospective nature of this study prevented collection of standardized data from all subjects. OCT-LAR was found to lower GH and IGF-1 levels without influencing glucose tolerance, while the effect on tumor shrinkage has still to be investigated. Further research, including a dose–response study, is required to investigate the changes in biochemical markers, clinical symptoms and tumor volume in response to OCT-LAR in patients with acromegaly.

In conclusion, our results suggest that OCT-LAR is a beneficial and safe therapeutic option for Japanese patients with acromegaly, at least as adjuvant therapy after surgical treatment.

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