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Forty Month Follow-Up of Persistent and Difficultly Controlled Acromegalic Patients Treated with Depot Long Acting Somatostatin Analog Octreotide

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Abstract. The objective of the present study was to investigate the effects of octreotide long acting release (S-LAR) preparation on GH and IGF-1 serum concentrations and pituitary tumor size in patients with persistent and difficultly controlled acromegaly even after adjuvant irradiation and/or dopamine agonists. Thirty-three patients with active acromegaly (26 female and 7 male, mean age; 43.94 ± 14.01 SD years) were included in this study. Patients were evaluated at baseline and at 6, 12, 30 and 40 months for GH, IGF-1, and GH response to OGTT and biliary ultrasonography. Sella MRI was performed at initial and at 40 months. All patients received 20 mg S-LAR. Afterwards, the dosage was titrated to improve individual GH response and reduction of IGF-1 into normal ranges. Basal serum IGF-1 levels decreased from median: 530 μg/l [IQR: 420–600] to 340 μg/l [IQR: 230–460] at 6 months ($p = 0.01$), to 400 μg/l [IQR: 222.4–600] at 12 months ($p = 0.48$), to 396 μg/l [IQR: 318–468] at 30 months ($p = 0.49$), to 482 μg/l [308–580] at 40 months ($p = 0.47$). Nadir GH levels in OGTT fell from 2.70 ng/ml [IQR: 1.35–6.90] to 1.60 ng/ml [IQR: 0.36–4.10] at 6 months ($p = 0.03$), to 0.31 ng/ml [IQR: 0.18–0.65] at 12 months ($p<0.0001$), to 1.50 ng/ml [IQR: 0.83–4.00] at 30 months ($p = 0.398$) and to 0.89 ng/ml [IQR: 0.58–1.35] at 40 months ($p<0.0001$). Initially, pituitary adenoma volume was median: 1.18 ml [IQR: 0.08–3.50] and it shrank to 0.21 ml [IQR: 0–2.1] at 40 months ($p = 0.08$). Gallstones were detected in 12 patients and six of them underwent cholecystectomy. S-LAR is an effective treatment regimen in reducing GH and IGF-1 concentrations and as well as in shrinking tumor volume in persistent and difficultly controlled acromegalic patients.

Key words: Acromegaly, Long term treatment, Sandostatin LAR

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ACROMEGALY is a chronic disease. In the majority of cases, acromegaly is caused by a growth hormone (GH) secreting tumor of the pituitary gland. It is associated with increased morbidity and reduced life expectancy, most commonly due to cardiovascular diseases [1]. All patients with acromegaly should receive therapy to stop progression of the disorder and to prevent late complications and excess mortality, as well. In acromegaly, the therapeutic goal is to restore normal growth hormone secretion dynamics, normalize serum insulin-like growth factor (IGF-1) concentration and shrink the pituitary mass, while maintaining the normal anterior and posterior pituitary functions [2]. Surgical resection of the pituitary adenoma is still the most cost-effective and rapid acting initial treatment choice for acromegaly. The cure rate of adenomectomy is 60–80% even if it is performed by the most experienced neurosurgeons; however, for larger tumors the success rate is 30–50% [3]. Therefore, patients who initially undergo surgical intervention require additional therapy, such as radiation, somatostatin analogs or dopa-

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mine agonists, to normalize GH and IGF-1 levels.

Somatostatin is an endogenous hypothalamic peptide that has a broad spectrum of regulatory functions in the body and inhibits GH release from the anterior pituitary. Octreotide is a synthetic somatostatin analog and was first used to treat acromegaly in the 1980s [4]. Octreotide therapy results in normalization of IGF-1 levels in approximately 50% of patients. Moreover, it has been demonstrated to induce tumor shrinkage in 30% of the patients [5]. However, the drug requires three times daily subcutaneous injections and has some gastrointestinal side effects, such as cholelithiasis. In 1998, a slow release, long acting form of octreotide S-LAR was developed to maintain a prolonged duration of GH/IGF-1 axis suppression [6]. This formulation is administered by intramuscular injection every 4 weeks, which increases the compliance of acromegalic patients.

The aim of this study was to investigate the Sandostatin LAR effect in patients with persistent disease after surgery, adjuvant irradiation and/or dopamine agonists, in a tertiary referral hospital in Istanbul, Turkey.

Patients and Methods

Thirty-three patients with active acromegaly (26 female and 7 male, mean age; 43.94 ± 14.01 SD years) followed and treated at Cerrahpasa Medical Faculty, Endocrinology and Metabolism outpatient clinic between 2000 and 2001 were included in this study. Last follow-up visit was performed in 2005. They had not received prior treatment with somatostatin analogues. Patients were enrolled into this study after their informed consent had been obtained. All the patients had persistent signs and symptoms of acromegaly after previous transsphenoidal surgery (n = 31), or surgery followed by gamma knife irradiation (n = 8), or combination of surgery and conventional radiotherapy (n = 6). The diagnosis of active disease determined by the presence of clinical findings and failure to suppress nadir GH level less than 1 ng/ml during OGTT and as well as high levels of IGF-1 adjusted for age and gender. Acromegaly was considered to be in remission, when both circulating IGF-1 level was within age and gender adjusted normal ranges and nadir GH was less than 1 ng/ml during OGTT [2]. Dopamine agonists were added to S-LAR treatment in twenty patients for their additive GH suppressive effect. Seven patients were treated with replacement therapy because of pituitary insufficiency. Six patients were lost to follow up and one patient died due to pulmonary tuberculosis. Among these seven patients, four completed the 30 month visit and three patients completed the 12 month visit.

Patients were evaluated for the presence of headache, arthralgia, perspiration, asthenia and acral and soft tissue overgrowth at the beginning and at 40 months by phone. In addition to seven patients who were lost during the follow-up, we could not reach three patients by phone, for symptom evaluation.

On the day of physical examination, blood samples were drawn for initial IGF-1, GH and insulin levels and GH levels were measured during the two hour 75 g. OGTT, as well. Insulin resistance was calculated with homeostasis model of assessment (HOMA-R) and less than 2.5 was considered to be normal [7]. Plasma GH levels were determined by IRMA (GH; Immunotech, Marseille, France; normal ranges; <10 ng/ml). IGF-1 levels were measured by IRMA after ethanol extraction using DSL kits (Diagnostic System Laboratories Inc. Webster, TX) in our laboratories. Data of normal IGF-1 ranges adjusted for age and gender in Turkish population are determined from the previous study of Tiryakioglu *et al*. [8]. Biochemical evaluation of patients was assessed at baseline and at 6, 12, 30 and 40 months of S-LAR treatment.

Ultrasonographic examination of the gall bladder and biliary system was performed at baseline and at 6, 12, 30 and 40 months. Magnetic resonance imagings (MRI) to evaluate tumor size, have been performed at baseline and at 40 months. Tumor size was evaluated in three dimensions by using DiChiro-Nelson formula [9]. Body mass index (BMI) kg/m^2 was evaluated at baseline and at the end of the study. The remnant tumor size after surgery was considered as baseline tumor size.

Twenty-four (72.7%) patients had macroadenoma. Nine (27.3%) patients had microadenoma. Cavernous sinus infiltration was observed in 13 (39.4%) patients.

After obtaining baseline blood samples, all patients were started on 20 mg S-LAR i.m. every 28 days. Following the third month of the therapy, the S-LAR dose had been titrated for each patient individually to achieve the goal of both normal IGF-1 ranges adjusted for age and gender and suppression of nadir GH levels to less than 1 ng/ml during a two hour 75 g. OGTT. The dose is titrated between 10–40 mg to achieve the

Table 1. Sandostatin LAR doses used during the study

S-LAR dose	Initial n (%)	6th month n (%)	12th month N (%)	30th month n (%)	40th month n (%)
10 mg	—	1 (3)	3 (9.2)	1 (3.3)	3 (11.5)
20 mg	33 (100)	29 (87.8)	9 (27.2)	10 (33.3)	3 (11.5)
30 mg	—	3 (9.2)	19 (57.6)	8 (26.6)	10 (38.4)
40 mg	—	—	2 (6)	11 (36.6)	10 (38.4)

Table 2. Clinical signs and symptoms of patients at baseline and at 40th month of the study

Symptom	At baseline (n = 33) (n)	40th month (n = 23) (n)	p
	25	5	0.001
Arthralgia	15	4	0.07
Perspiration	14	1	0.004
Asthenia	16	2	0.004
Acral growth	29	4	<0.0001

therapeutic levels at 6, 12, 30, and 40 months (Table 1).

SPSS software program was used for statistical analysis. The results were defined as median and interquartile ranges. Statistical analysis of the data was performed by Wilcoxon, Friedman. McNemar test was used when appropriate. A $p<0.05$ value was accepted as statistically significant.

Results

Clinical signs and symptoms of all patients improved significantly during the therapy (Table 2).

Random GH values decreased from median 4.3 ng/ml [IQR: 2.20–7.60], to 2.2 ng/ml [IQR: 0.94–5.35] at 6 months ($p = 0.01$), to 0.5 ng/ml [IQR: 0.20–1.10] at 12 months ($p<0.0001$), to 2 ng/ml [IQR: 1.30–5.40] at 30 months ($p = 0.58$) and to 1.10 ng/ml [IQR: 0.89–2.75] at 40 months ($p<0.0001$). Serum IGF-1 levels decreased from median: 530 µg/l [IQR: 420–600] to 340 µg/l [IQR: 230–460] at 6 months ($p = 0.01$), to 400 µg/l [IQR: 222.4–600] at 12 months ($p = 0.48$), to 396 µg/l [IQR: 318–468] at 30 months ($p = 0.49$) and to 482 µg/l [IQR: 308–580] at 40 months ($p = 0.47$) (Fig. 1). Nadir GH levels during a two hour 75 g. OGTT fell from 2.70 ng/ml [IQR: 1.35–6.90] to 1.60 ng/ml [IQR: 0.36–4.10] at 6 months ($p = 0.03$), to 0.31 ng/ml [IQR: 0.18–0.65] at 12 months ($p<0.0001$), to 1.50 ng/ml [IQR: 0.83–4.00] at 30 months ($p = 0.398$) and to 0.89 ng/ml [IQR: 0.58–1.35] at 40 months ($p<0.0001$) (Fig. 2).

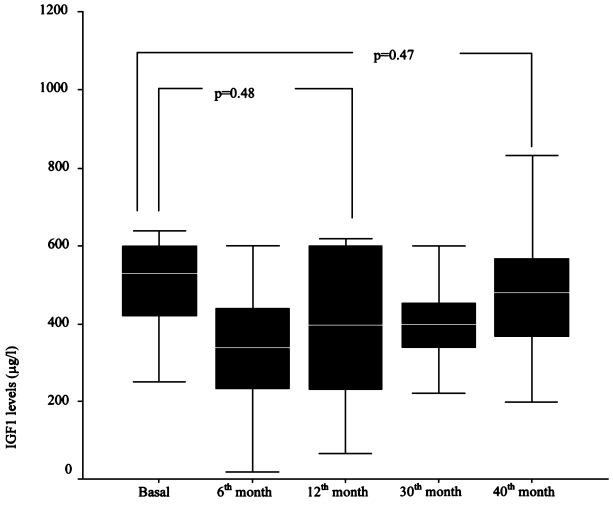

Fig. 1. Serum IGF-1 values before and during the therapy

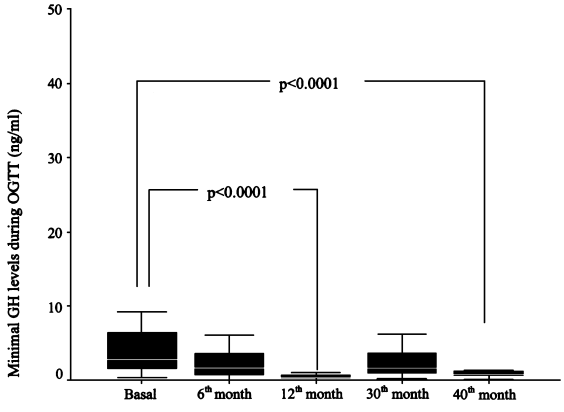

Fig. 2. Serum nadir GH values in OGTT before and during the therapy

We observed no age, gender and gonadal status differences in GH and IGF-1 values at the baseline and in the long term follow-up. We could not find any differences in IGF-1 and GH values when we analyzed the data according to tumor volume and the existence of radiotherapy treatment. We observed no difference in IGF-1 values between invasive patients and noninvasive patients. Nadir GH levels were higher at 6 and 12 month in invasive patients ($p = 0.042$ and $p = 0.06$ respectively).

Remission rate was 35.4% at 6 months, 83.8% at 12 months, 31.8% at 30 months and 60% at 40 months according to the suppression of GH levels to less than 1 ng/ml during two hour 75 g. OGTT. Remission rate was 37% at 6 months, 34.6% at 12 months, 43% at 30 months, and 28.5% at 40 months according to achievement of normal IGF-1 levels adjusted for age and gender. When remission of disease was considered to be both achieving the nadir levels of GH of less than 1 ng/ml during OGTT and normal IGF-1 levels adjusted for age and gender, remission rate was as follows: 34% at 6 months, 33% at 12 months, 17% at 30 months, 28% at 40 months. Discordant results between GH and IGF-1 were observed in 41% of patients in our series.

Diabetes was observed in 9 (27%) patients during follow-up period. BMI and the insulin sensitivity index HOMA-R did not change during the follow-up ($p = 0.22$, $p = 0.75$, respectively).

Prior to the study, the pituitary adenoma volume was median 1.18 ml [IQR: 0.08–3.50] and it shrank to 0.21 ml [IQR: 0–2.1] at 40 months ($p = 0.08$).

Gall bladder ultrasound examinations revealed gallstones in 12 patients. Six of 12 patients had undergone to laparoscopic cholecystectomy.

Discussion

This study demonstrates the efficacy and safety of long term S-LAR treatment during a 40 month period in acromegalic patients who had persistent disease after surgery. Fluctuations were observed in levels of IGF-1 and in nadir levels of GH during OGTT in the follow-up period. However, both GH and IGF-1 levels were significantly lower during 40 months of follow-up period when compared to the pretreatment state.

The ideal therapy for acromegaly should normalize GH suppression and achieve IGF-1 levels within normal ranges adjusted for age and gender, and it should block tumor growth and even shrink it while maintaining normal secretion of other pituitary hormones. It should be safe, cost effective and have few side effects, as well [10]. The cure rate of surgery is 60–80%; for larger tumors the success rate falls down to 30–50% [3]. In our institute, all the transsphenoidal surgical procedures were performed by the same neurosurgeon and post surgical remission rate was 51% [Unpublished data]. It has been widely shown that somatostatin analogues act rapidly and reduce GH and IGF-1 concentrations effectively [11]. The availability of slowly released S-LAR formulations has further improved patients' compliance to long term treatment of acromegaly.

In a previous study, it was shown that S-LAR treatment suppresses GH secretion in 71.4% of patients and normalize IGF-1 secretion in 67.8% of patients [Unpublished data]. A metaanalysis published recently, reported safe GH levels in 56% of patients and IGF-1 normalization in 66% with monthly injections of S-LAR [12].

Although 39.4% of our patients had invasive adenoma and all needed multimodal therapy to achieve the strict therapeutic goals, our data confirmed the effectiveness of S-LAR in controlling hormonal hypersecretion in difficultly controlled acromegalic patients. In accordance with previous studies [13, 14] the results of the present study showed that treatment with S-LAR is highly effective in controlling GH and IGF-1 hypersecretion in the majority of the cases (60% and 28.5%, respectively). Our remission rate for achieving safe GH values was better than achieving safe IGF-1 levels.

Discordance between rates of achieving safe GH levels and IGF-1 levels was observed in 41% of our patients and this contradiction had been reported previously in different series. Cozzi *et al*. [10] and Wass [15], showed 23% and 19% discordance in their series. Monteras *et al*. reported a higher discordance rate of 33% in patients with microadenoma [16]. They suggested that this discordance was a consequence of persistent, but continuously released low levels of GH secretion that is capable of inducing an exaggerated stimulation of IGF-1 synthesis [17]. The concomitant finding of normal IGF-1 level and pathological GH level could be putatively explained by a hypothesis of treatment-induced loss of biological activity of the GH molecule [10]. We observed a slightly higher discordance in our study. Although our patients are under

treatment, they have higher GH responses to OGTT than normal population. Due to their supraphysiological GH responses, their IGF-1 stimulation may be exaggerated. Age and gender related reference ranges for IGF-1 are relatively broad, and our data could support the existence of individual IGF-1 response. It has been shown that by using more sensitive and specific assays, nadir GH levels after OGTT were less than 0.14 μg/L in healthy adults [18]. Consequently, even though safe considered suppressed GH levels may be supraphysiologic and may result in higher IGF-1 stimulation. Using more sensitive and specific assays in patients with invasive adenoma or patients who need additional therapeutic modalities after surgery, similar to our study group, may lower discordant GH and IGF-1 values. Further population-based studies are needed to confirm these findings.

We observed no gender, age and gonadal status differences in GH and IGF-1 values at the baseline and in the long term follow-up. In a previous study Colao *et al*. reported similar data with our study [19].

We observed no difference in IGF-1 values between cavernous sinus invasive and noninvasive patients. Although nadir GH levels were higher at 6 and 12 months, ($p = 0.042$ and $p = 0.06$ respectively) in patients with cavernous sinus invasion, this difference did not exist at 30 and 40 months. Patients with cavernous sinus invasion were difficult to control compared to the noninvasive patients. In the invasive patient group S-LAR doses were higher than the noninvasive group. At 40 months 37.5% of the invasive patients were using 40 mg S-LAR while only 10% of the noninvasive patients were using 40 mg S-LAR.

We found a significant improvement in our patients' clinical symptoms and signs. However, our observation on signs and symptoms are limited because our assessment was not based on an analogue scale or include a quality of life scale. Nevertheless, in accordance with another study with S-LAR [20] all our patients reported improved compliance and reduction of their symptoms.

There were no differences between in HOMA-R values before and after treatment. In a previous study it has been shown that S-LAR treatment for 6 months decreases HOMA-R values similar to healthy subjects [21]. We did not observe a significant weight loss during the study. This might be the reason for the unchanged HOMA-R values.

We observed significant tumor shrinkage in our study group. Different rates of tumor shrinkage during S-LAR treatment were reported ranging from 17% to 43%. *De novo* patients' tumor shrinkage was up to 80% [12]. Oshino *et al*. reported that, occurrence of tumor shrinkage with octreotide treatment is relevant to a good response to both bromocriptin and octreotide challenge test. They also showed that preoperative octreotide treatment is effective in tumor volume reduction in 52% of patients with mean reduction to 68% of the initial volume [22]. In our study, we observed a significant tumor reduction, but it was not correlated with biochemical control. In accordance with our study, it was shown that octreotide induced tumor shrinkage does not always correlate with biochemical control [23, 24]. Amato *et al*. reported that somatostatin analogues caused significant shrinkage in GH secreting adenomas and that such shrinkage was not correlated with control of GH secretion. They explained this situation with the different mechanisms that regulate antimitotic and antisecretory actions of somatostatin analogues [4]. On the other hand, Colao *et al*. reported that postoperative IGF-1 values were highly correlated with the tumor size [25]. Conflicting reports of octreotide on tumor volume may be due to the existence of different study designs, heterogeneous patient groups and imaging techniques. In our study, most of our patients had been treated with surgery and radiotherapy. Remnant tumor sizes were considered as baseline tumor sizes. The irregularity of the remnant tumors, caused by fibrosis and histological changes, does not allow a precise estimation of the tumor size with MRI.

Incidence of side effect was scant, and patients' compliance to the long-term treatment was excellent even in patients treated with 40 mg S-LAR every 28 days. However, the incidence of cholelithiasis was relatively high in our patients. In 12 patients gallstones were detected and 6 of them underwent laparoscopic cholecystectomy. In a previous study S-LAR treatment was found to be associated with gallstone development in up to 20% of patients; however, duration of the follow-up in this study was not as long as our study [26].

In conclusion, our results suggest that S-LAR treatment is effective and well tolerated treatment for acromegalic patients and can be successfully applied as a secondary therapy for acromegalic patients with persistent active disease after previous transsphenoidal surgery and/or radiotherapy.

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