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The Effect of Sandostatin LAR in the Treatment of Acromegaly

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Abstract: This study was designed to investigate the effects of sandostatin LAR after multiple injections and duration of its effect on acromegal patients. Five acromegal patients were treated with sandostatin LAR. After performing Octreotide test, 30 mg sandostatin LAR was administered for 3 times and the frequency of mean daily Growth Hormone (GH) less than $5 \mu\text{g L}^{-1}$ were compared between 1st and 3rd injections. Then drug's acting period was assessed ($\text{G.H} < 5 \mu\text{g L}^{-1}$). In addition in 3 patients the efficacy of 30 and 40 mg daily dosages were compared with each other. No significant relationship was found between the response rate to sandostatin and short acting Octreotide. Also the frequency of $\text{GH} < 5 \mu\text{g L}^{-1}$ after 3rd injection was more than scale after the first injection ($p < 0.01$). The drug's effect continued for at least 42 days after injections. Octreotide test (with single dose injection) wasn't proved to be a reliable method for prediction of patients' response to treatment. Measuring GH after multiple injections is a better method for this purpose and it's also better to determine injection intervals in each patient individually.

Key words: Acromegaly, sandostatin LAR, growth hormone

INTRODUCTION

Therapeutic methods for treatment of acromegaly have undergone major alterations during recent years. The success rate of surgery has been variable depending upon surgeon's experience and tumor size and extension^[1-3]. Due to the silent nature of the disease, its diagnosis may be missed for up to 10 years or even more^[4,5]. Thus in most of the cases adenoma's diameter will be in the range of macro adenoma upon diagnosis and surgery may not be successful in more than 50% of such cases^[6]. These problems have been the reasons of extensive efforts to search for alternative treatments for this disease.

Somatostatin is an endogenous inhibitor of Growth Hormone (GH) secretion with a short half life. Octreotide, a long acting analogue of somatostatin has been a successful treatment for acromegaly^[7,8]. Due to the relative short half life of octreotide (nearly 2 h), multiple daily injections of the drug are needed to control GH secretion.

Sandostatin LAR is produced by adding soluble polymers to octreotide. The drug's half life is considerably more than octreotide and its efficacy has been proven in multiple studies but rare investigations have been conducted about the action duration of this product^[9-12].

For treating acromegaly, injections at 6-week intervals have the same result as of 4-weeks in suppressing GH secretion^[13]. Early diagnosis and treatment of the disease will lead to reversal of most of the side effects including cardiomyopathy. It was seen in a study that cardiomyopathy disappeared in young patients who used sandostatin LAR for one year^[14]. GH and Insulin Growth Factor-1 (IGF1) normalization after sandostatin LAR, leads to a decrease in joints thickness. IGF1 suppression also decreases tissue hypertrophy in acromegal patients' joints^[15].

The use of long acting somatostatin analogues reduces GH levels to less than $2 \mu\text{g L}^{-1}$ in 50-65% of cases. Also in 65% of patients IGF1 levels were in normal range. It was shown that although one year use of long acting somatostatin didn't change the result of Glucose Tolerance Test (GTT) significantly, but in some patients there was some problem with this test which makes long term glucose monitoring advisable^[11]. Another study showed a reduction in hypophysis tumor size after one year use of sandostatin in 37% of patients. Also symptoms such as severe headaches, perspiration, arthralgia, extremities swelling and fatigue reduced significantly and even disappeared in some cases^[16]. In acromegal patients whom previous treatments have failed or with any treatment contra indication, sandostatin LAR

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is the treatment of choice^[17]. In this study, we investigated the efficacy and duration of action of sandostatin LAR in acromegal patients.

MATERIALS AND METHODS

This study was conducted on 5 acromegal patients admitted to clinic of endocrinology in Shariati Hospital of TUMS. The diagnosis of acromegaly was built upon these three factors: 1-Absence of growth hormone suppression to less than 2 µg L⁻¹ following intake of 75 g glucose, 2-IGF1 levels higher than normal and 3-Adenoma in hypophysis MRI. Patients were included in the study only if their last scalp radiotherapy was done more than one year before the study. All patients were informed about the study protocol and their consent obtained inclusion in the study.

From one month before the study patients stopped using dopaminergic drugs and octreotide. After one month of washout, hypophysis MRI, liver sonography, thyroid function tests (T₃, T₄ and TSH) and prolactin test, were done. The blood sampling with 2 h intervals was carried out for 24 h in order to determine average GH level. At the end of the first day of the study octreotide test was performed with the following method: 200 µg octreotide was injected intradermally and then 3 samples were obtained with 2 h intervals to measure GH level. Then the patients were included in the study regardless of their test results. In all patients sandostatin LAR was prescribed as three 30 mg vials of intra muscular injections that were injected with 63 days intervals. Twenty four hour GH profile was also obtained on days 0, 14, 28, 35, 42, 49 and 63 after each injection. In order to determine the duration of action of the drug, GH measurement continued after the day 63 of the third injection with one week intervals.

In the second stage of the study, 3 patients were treated with 40 mg dosage instead of 30 mg, in order to compare the effectiveness and duration of action of 30 and 40 mg dosages. Patients of this group were the same patients that included in the study after passage of the wash out period of the drug which considered being 3 months^[18]. At the end of the study, hypophysis MRI, liver sonography and thyroid function tests (T₃, T₄ and TSH) were repeated.

GH measurement was done with RIA method by SPECT RIA kits with normal range of 5 to 14 µg L⁻¹. Interassay and intrassay of GH measurement was 8.8% and 1.9%, respectively. Average GH levels in days 14 to 49 were compared between 1st and 3rd injections in 30 mg dosage group. Also a comparison between the result of 30 and 40 mg dosage in the third injection was done using t-test. The frequency of GH amounts less than 5 µg L⁻¹

after the first and third 30 mg injections were compared using Fisher exact test.

In this case series SPSS-11.5 was used for statistical analysis. For comparing results of octreotide test and sandostatin (Table 1), Wilcoxon's test was used for comparing GH amounts between the first and third injections (Table 2), McNemar's test was also used.

RESULTS AND DISCUSSION

In this study 5 patients (4 females and 1 male) whose ages were between 23 and 42 years and had undergone transsphenoidal hypophysectomy, were included. Three of them had undergone scalp radiotherapy. Octreotide test results are shown in Table 1. There was no significant relationship between the percentage of GH reduction after test and the 24 h average GH levels in days 14 to 49 after 30 mg dosage injection. GH measurement continued after the 63rd day of the third injection in order to determine the duration of action of sandostatin LAR.

The average 24 h GH secretion on days 14, 28, 35, 42, 49 and 63 after the first and 3rd injections are shown in Fig. 1 and 2. Table 2 shows the frequency of GH <5 µg L⁻¹ after first and 3rd injections. In all the patients whose 28th day GH averages were less than 5 µg L⁻¹ (4 patients), GH suppression continued for at least 14 days after the day 28. In patient no.3 this suppression continued for 21 months after the end of treatment. In patients No. 1 and 5, GH levels remained less than 5 µg L⁻¹ until days 84 and 70, respectively. Three patients (No. 1, 4 and 5), were treated with 40 mg dosage. However average GH level, duration of action and GH <5 µg L⁻¹ frequency didn't show significant difference in the 30 mg dosage group.

The effectiveness of octreotide and its long acting products (sandostatin LAR, lanreotide) in the treatment of acromegaly has been shown in different studies^[7-13]. In this study the 24 h GH average in days 14 to 49 after the first and 3rd injections with 30 mg dosage showed a

Table 1: Comparison between responses to Octreotide test and sandostatin

Case	Basal GH (µg L ⁻¹)	GH level after Octreotide test (µg L ⁻¹)	GH level after sandostatin LAR (µg L ⁻¹)
1	21.3	17.0	2.50
2	12.2	9.0	8.90
3	99.0	5.1	3.30
4	20.9	2.0	15.20
5	25.6	9.0	7.80

Table 2: Frequency of GH <5 µg L⁻¹ in the first and third injections

Case	First injection (%)	Third injection (%)
1	100	100
2	0	66
3	100	100
4	0	20
5	0	100

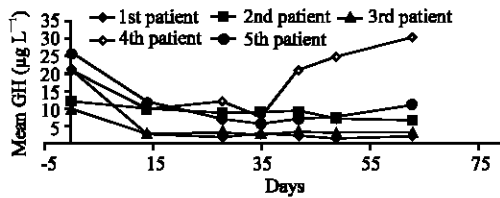


Fig. 1: Twenty four hour GH mean in days after the first injection (30 mg)

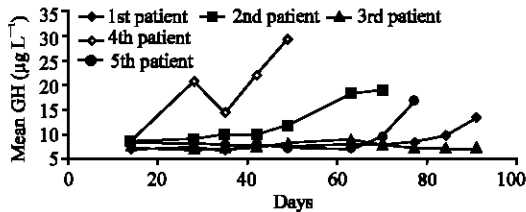


Fig. 2: Twenty four hour GH mean in days after the third injection (30 mg)

decrease of 58 and 70%, respectively in comparison with basal GH average and the relative frequency of GH levels less than 5 µg L⁻¹ in days 14 to 49 after the 1st and 3rd injections were 40 and 80%, respectively.

In one study it was reported that octreotide usage lead to GH reduction in 90% of patients and in 40 to 50% lead to reduction of GH to less than 10 µg L⁻¹[17]. Octreotide continuous infusions caused more suppression in 24 h GH levels[18]. In another study, the effect of sandostatin LAR in 24 h GH suppression has been similar to intradermal octreotide but its effect on reducing fasting GH was more than that[19].

Different studies have evaluated the variable therapeutic responses to Octreotide and sandostatin. One study[17] showed that treatment with Octreotide causes progressive GH suppression. In another study[20], multiple injections increased duration of drug action and serum level 1.6 times more than single injection.

Four weeks interval has been proposed for sandostatin injection by the product manufacturer but in our study we saw that in patients who showed response to 30 mg dosage, the duration of action of sandostatin LAR was considerably more than 4 weeks. In one study it has been reported that therapeutic effect of sandostatin LAR was equal in 4-week and 6-week interval injections[13]. In the study conducted by another group[21], serum GH average was less than 5 µg L⁻¹ in 72% of patients 4 weeks after sandostatin LAR prescription. When these 72% were followed for another 2 weeks, it was seen that GH level remained less than 5 µg L⁻¹ in 92% of them. In another study[22], GH amount remained low until day 42 in 4 patients (out of 8) but in the other 4 patients the GH began to rise after the day 35. In the day 60 after the

injection, GH increased in 6 out of 8 patients. In another study[22], the follow up of 12 patients showed these results: The growth hormone picked up at 4-8 weeks in 5 patients and in remaining such increment happened between weeks 8-12. One report[23], showed that GH level remained lower than 5 µg L⁻¹ in all 8 studied patients for more than 6 weeks after injection of 30 mg dosage of sandostatin LAR.

According to the findings of this study and the previous ones and because of the high cost of the drug, it seems logical to determine injection intervals for each case individually. In our study octreotide test was done before drug prescription and there wasn't significant relationship between GH average after the test and the rate of patient's response to sandostatin LAR. We also claim that according to the results obtained in the present study, the octreotide test (with the method of single injection and measuring GH average from 3 measurements with 2 h intervals) is not an appropriate test for patient selection for treatment with sandostatin LAR although studies with bigger sample sizes may reveal other results.

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