RESEARCH ARTICLE

Response of Patients with Acromegaly to Long-acting Octreotide with regard to Regression of Pituitary Adenoma, Growth Hormone and Insulin-like Growth Factor-1

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ABSTRACT

Introduction: Acromegaly is a rare endocrine disease; its treatment is surgical (Hypophysectomy). However, somatostatin analogs represent another modality of therapy in addition to deep X-ray therapy as a third, option. The aim of the study is to find out the response of patients with acromegaly to octreotide as reflected on regression of adenoma size, insulin-like growth factor (IGF), and growth hormone (GH) by studying the medical records of many patients with acromegaly.

Method: A total of 80 patients with acromegaly are enrolled in the study from July/2019 to April/2020. Their age range (20–72 years). They are 47 men and 33 women. Their selection was based on their visits to NDC on the basis of prescheduled appointments to be given their monthly injections of long-acting octreotide (LAR) and to be examined clinically plus conducting various types of hormonal studies and biochemical workups to assess their response to treatment on the following parameters: Adenoma size, IGF-1 and GH and its correlation with octreotide dose.

Results: It is a cross-sectional comparative clinical trial study of 80 patients with acromegaly. Mean of age was 46.7 ± 12.4 years', and their age range (20–72 year) minimum and maximum-year-old. Mean duration of taking drug was 8 ± 6.7 years. The mean of total LRA injection was (1073.6 ± 666.2 mg). 58.75% of patients were male while 41.25% were female. 46.25% of patients do not have transsphenoidal direct surgery, but 46.25% undergo one surgery, 7.5% undergo two transsphenoidal hypophysectomies. 87.5% of patients have no gamma knife while 12.5% have gamma knife radiosurgery.
Conclusion: Acromegaly is a multi systemic disease that should be diagnosed and treated as early as possible to prevent complications and improve mortality rates.

Keywords: Acromegaly, Long-acting octreotide, Pituitary adenoma, Growth hormone, Insulin-like growth factor-1.

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INTRODUCTION

Acromegaly is a rare chronic hormonal disease characterized by overproduction and secretion of growth hormone (GH) and subsequently elevated Insulin-like growth factor (IGF-I) blood levels,[1] Leading to a progressive somatic disfigurement and a wide range of systemic manifestations.[2] Medical treatment is designated for patients with determined illness despite operating remove of the adenoma. The SRLs "octreotide, lanreotide and pasireotide, as well as the dopamine agonist cabergoline", defeat GH excretion.[3] The effectiveness rates are parallel for the two long-acting drugs[4] but guidance management might select a favorite for way of transfer and related cost.[5] Pasireotide LAR and octreotide LAR have a parallel consequence of tumor decrease, although pasireotide was greater than octreotide in biochemical control.[6,7] We should recommend cabergoline to is a second-line treatment in patients resistant SRL treatment or in a mixture with SRLs in partly resistant patients. It is also a potential management choice in patients with acromegaly with problematic to control diabetes mellitus.[8,9] The American guidelines recommend measuring a random GH (and an IGFI level) at ≥ 12 weeks from surgery, while GH after OGTT only be measured if GH > 1-µg/L.[10] Disease remission is defined with undetectable post-operative random GH. Published data consider remission once the disease is under control and random GH value is < 1-µg/L. As stated in guidelines,[11] disease remission is also determined with a post-operative

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GH level with OGTT of < 1 or ≤ 0.4 µg/L. with apparently complete resection, if IGFI value is > 1.5 but < 2 ULN, 3 months after surgery, there should be repeated IGFI at 1 to 3 months according to guidelines,[11] and to determine GH after OGTT before initiating treatment directly. Pituitary MRI follow-up is conducted after 6 months of pegvisomant treatment and 6 to 12 months of SSA treatment.[12] The aim of study is to find out the response of patients with acromegaly to octreotide as reflected on regression of adenoma size, IGF, and GH by studying the medical records of many patients with acromegaly.

MATERIALS AND METHODS

For 80 patients with acromegaly registered In the National Diabetes Center (NDC) Mustansyrriah University Baghdad Iraq, are enrolled in the study from July/2019 to April/2020. Their age range (20–72 year). Inclusion criteria: previously diagnosed patients with acromegaly attending the NDC regularly to take their monthly injections. Exclusion criteria: patients with irregular visits, discord follow-up program regimen, missed medical, biochemical or radiological reports, and responsive patients who stop receiving treatments. Most diagnosis was already done in NDC depending on biochemical markers (IGF- 1 and GH value with oral glucose tolerance test) and radiological features on MRI reports that reserved and reported in individual documents for each patient, including other personal, surgical and medical history. Biochemical studies were done for every patient with high clinical suspension of acromegaly after a complete history and clinical examination to confirm diagnosis and then for follow-up medical or surgical response, these include GH level with OGTT; with a diagnostic cutoff value of (> 1-ng/mL), IGF-1 level; with a diagnostic age-matched cutoff value of (>200–450 ng/mL) for patients >18 year old and (>165–620 ng/mL) for patients 10 to 18 year old. The blood sample was drown, centrifuged and refrigerated in deep freeze for hormonal measurements using the principle of chemiluminescence assay. Statistical analysis done by SPSS 22, frequency and percentage used for categorical data, mean, median and SD for continuous data. Chi-square used for the assessed association between variables. Person correlation shows the correlation between continuous data. ROC curve also used to show more specific and sensitive cutoff point. *p-value* less or equal to 0.05 is consider significant.

RESULTS

Cross-sectional descriptive clinical trial study of 80 patients with acromegaly, mean of age was 46.7 ± 12.4 years' old (20–72) minimum and maximum year old. As shown in the Figures 1, 2 and 3, 46.25% underwent one surgery, 41.25% showed no regression in adenoma size, but 33.75% showed regression from macro to microadenoma, and 21.25% of their adenoma disappeared and became normal on MRI and finally, 3.75% show empty Sella. Duration of disease 80% of patients have duration 1 to 10 years.

Respond to LAR by regression of GH level, in those treated for 1 to 10 years the respondent 41 (51%) out of the 64 (80%) patients and 9(11.3%) patients out 12(15%) patients in those treated for 11 to 20 years while all patients 4(5%) treated for 21 to 30 years attain the proposed goal of GH level but these differences did not reach statistical significance (p=0.27). as in Table 1.

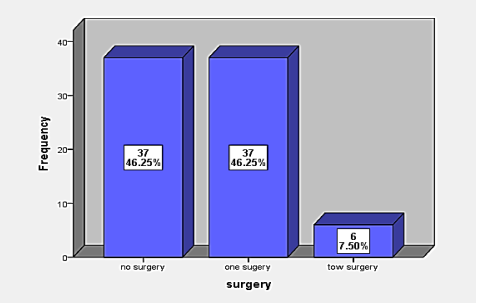

Figure 1: Tran sphenoidal hypophysectomy

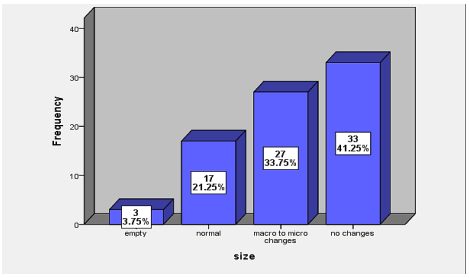

Figure 2: Regression of adenoma by ≥ 20 of largest dimension

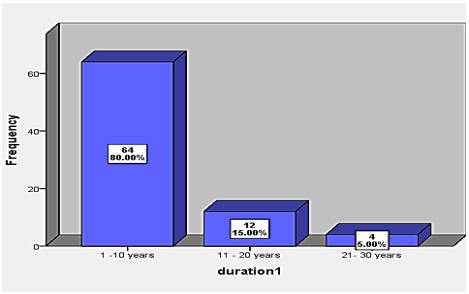

Figure 3: Duration of treatment with monthly long-action octreotide injections

Adenoma size regression in respondents to LAR injection in the presence of hypophysectomy 1 or 2 times and in the absence of history of hypophysectomy. In those with no preview surgery, 1 (1%) out of 37 (46%) developed empty Sella, 15 (19%) out of 37 (46%) their adenoma regressed from macro to micro, 7 (9%) out of 37 (46%) have pituitary regression to normal. So, the respondent is 23 (29%) out of 37 (46%). In those with single surgery 1 (1%) out of 37 (46%) develop empty Sella, 11 (14%) out of 37 (46%) have adenoma regression from macro to micro. In comparison, 9 (11%) out of 37 (46%) have quit normal pituitary gland MRI, so respondents are 20 (26%) out of 37 (46%) patients Table 2. In those treated by tow hypophysectomy 1 (1%) out of 6 (7.5%) develop empty Sella, 1 (1%) out of 6 (7.5%) have adenoma regression from macro to micro, 1 (1%) out of 6 (7.5%) have normal pituitary gland MRI. although, all these changes not reach to statistical significant p=0.59. So, the surgery has no impact on the response to LAR

Table 1: Association of duration with GH response

response *no response*			*GH*		*Total*
Duration	1–10 years	Count	41	23	64
		% of Total (%)	51.3	28.8	80.0
	11–20 years	Count	9	3	12
		% of Total (%)	11.3	3.8	15.0
	21–30 years	Count	4	0	4
		% of Total (%)	5.0	0.0	5.0
Total		Count	54	26	80
		% of Total (%)	67.5	32.5	100.0

p-value = 0.27 (not significant)

injection regarding adenoma regression and development of empty Sella.

Figures 4 and 5 show the ROC curve against sensitivity and specificity. ROC curve revealed the best dose for target achievement by adenoma size regression by ≥ 20% of its longest diameter and IGF-1 down to normal age and gender match non-acromegaly counterparts and GH decrease down to ≤ 2.5 ng/l is 545 mg. The cumulative dose of LAR with (81.5% sensitivity and 53.8% specificity) (Table 3).

DISCUSSION

Serum GH concentrations are classically raised but levels may vary extensively. The initial test gauges serum IGF-1 in a patient with clinically supposed acromegaly.[10] In the current studies, there is clear differences in GH and IGF-1 concentrations according to gender in either healthy persons as well as patients with acromegaly.[13, 14] usually females in the premenopausal period produce greatly more GH than usual men or postmenopausal females to reach equivalent IGF-I levels.[15] This comparative GH resistance is because direct estrogen effects on liver IGF-I production.[16] our study confirms the significant association between LAR treatment duration and tumor size regression on MRI. Information on long-term SSA management on tumor decrease are very inadequate. In patients with obtainable MRI,[17] tumor reduction happened in 10 of 11 *de novo* (91%). Tumor size reduction is reported in

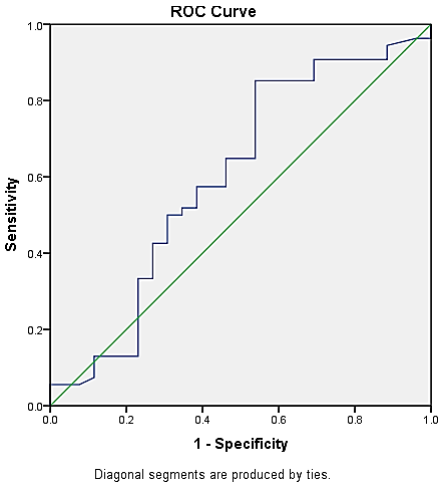

Figure 4: ROC curve against sensitivity

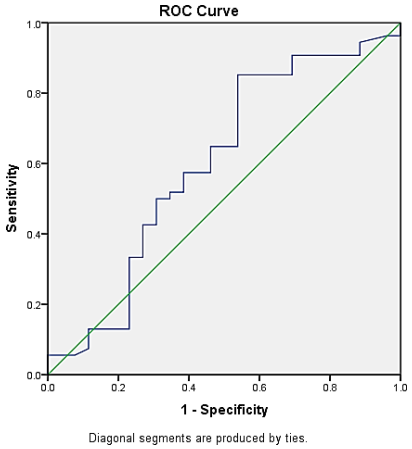

Figure 5: ROC curve against specificity

77% of 51(105), 82% of 55 patients by cozzi *et al.*,[18] and 43% of 21 patients treated for at least 30 months up to 18 year: in two patients with microadenoma and one with macroadenoma, the tumor disappeared.[18] In line with others,[19] we reported a mean reduction in tumor volume by 46% with 75.7% of 99 patients having tumor shrinkage greater than 25% after 1-year of treatment with further shrinkage by 35.3–13.1% during the second year of treatment.[20] According to ROC curve, the

Table 2: Association of transphenoidal surgery with change in size of the tumor under MRI

empty normal			Size				Total
			macro to micro changes	no changes			
Surgery	no surgery	Count	1	7	15	14	37
		% of Total (%)	1.3	8.8	18.8	17.5	46.3
	one surgery	Count	1	9	11	16	37
		% of Total (%)	1.3	11.3	13.8	20.0	46.3
	tow surgery	Count	1	1	1	3	6
		% of Total (%)	1.3	1.3	1.3	3.8	7.5
Total		Count	3	17	27	33	80
		% of Total (%)	3.8	21.3	33.8	41.3	100.0

p-value = 0.59 (not significant)

Table 3: Cumulative dose of LAR with sensitivity and specificity

Level (mg)	*Sensitivity (%)*	*Specificity (%)*
545	81.5	53.8
570	79.6	53.8
605	77.8	53.8

best accumulative dose of LAR for targets achievement, by adenoma size regression by ≥ 20 % of its longest diameter and IGF- 1 level down to normal age and gender match non-acromegaly counter and GH decrement down to ≤ 2.5 ng/l was 545 mg with 81.5% sensitivity and 53.8% specificity. This study shows significant association of LAR total dose with IGF-1 level decrement but no significant association with neither GH decrement nor pituitary tumor size reduction. If given as primary or secondary treatment, octreotide LAR treatment will control IGF-1 level effectively(with in normal level) in 100% of patients with acromegaly. Velija *et al.*[21] a retrospective study results show that long term treatment with octreotide LAR (given as first line treatment or as combination therapy), the normal level of IGF-1 is reported in 75% of patients[17] and long term progressive normal level of IGF-1 have been recorded during this study (61% at 1 years, 68% at 2 years and 79% at 3 years). A total of 50 to 80% of patients have well-controlled IGF-1 level with LAR treatment.[22] A network meta-analysis was built for the outcome number of patients who achieved IGF-1 control, including seven of the reported trials and five drugs (lanreotide, lanreotide autogel, octreotide LAR, pasireotide, and pegvisomant) and placebo. All these trials considered that IGF-1 levels were controlled when normal values were observed after taking into account patients' age and sex.[23] There are many different immunoassays for GH and IGF-1 level measurements but with wide different characteristics that may cause variable results. Various studies present a wide range of data about biochemical control of disease with octreotid-LAR over years. Study show that significantly greater reduction of serum IGF-1 concentrations when receiving preoperative octreotide LAR treatment than patients who initially underwent surgical treatments.[24] Also, (Zeinalizadeh *et al.*) disagreed with others and showed that preoperative SSA medical therapy significantly increases the success rate of surgery regarding to GH level but decrease effectively IGF1.[25] IGF1 level are age-adjusted but GH response value (2.0–2.5 mg/l) is usually age independent. colao *et al.* recently report that elderly patients should have lower fasting GH level (i.e 1.4 mg/l), which explains disproportionate records between GH and IGF-1 value.[26] Most recent studies about tumor volume response to LAR treatment documents cutoff of 20 to 25% volume reduction to be of significant response and lower limit are unlikely to be determined due to variable methodology. For patients with macroadenoma, the preoperative LAR treatment not shown to increase overall surgical remission rate and the success rate decreased substantially with large, invasive tumor and other management options are indicated if LAR treatment failed.[27] Other studies show that male patients and para sellar extention significantly predict persistent disease.[28]

CONCLUSION

Reduction of IGF-1 down to normal age and sex-matched control was found among patients with acromegaly between 41 to 50 years of age as the best age range, respondents to LAR by IGF-1 regression was found in 67.5%, while only 55% responded by adenoma shrinkage and 67.5 % by growth hormone GH decrement down to ≤ 2.5 mg/l, men are better respondents than women and prolonged use of LAR is found to be useful to achieve the proposed goals.

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