Octreotide Dose Escalation as Primary and Secondary Therapy for Patients with Acromegaly

A Clinical Study

Abbas Mahdi Rahmah* FRCP**, Nizar Shawky Shawky** CABM**, Noor Thair Tahir*** PhD

ABSTRACT

Background: Acromegaly is known to reduce life expectancy. Predictors of survival are growth hormone (GH) ≤ 2.5 µg/L and normal insulin like growth factor-1.

Objective: To evaluate efficacy of dose escalation of octreotide – long – acting – repeatable from 20 to 40 mg every 28 days intramuscularly in a sample of acromegalic patients whose biomarkers fail to drop down to the recommended targets after using octreotide – long – acting – repeatable for a year (20 mg) every 28 days.

Methods: An analytic, observational, open and prospective study. Seventeen acromegalic patients using octreotide – long – acting – repeatable 20 mg every 28 days fail to reduce growth hormone < 2.5 µg/L and insulin like growth factor-1 to the recommended level. The dose was doubled for six months, in order to achieve the recommended goals of growth hormone and insulin like growth factor-1.

The patients were divided into two groups in each occasion:

- Those harbouring microadenoma versus macroadenoma.
- Patients with previous hypophysectomy versus those with no prior hypophysectomy.
- Males versus females.
- Those with a disease duration ≥ 10 years versus those with a disease duration of < 10 years.
- Sonogram of the abdomen and oral glucose tolerance test were done prior to recruitment and at the end of the study.

Results: Growth hormone and insulin like growth factor-1 levels drop by 62.5% and 37%, respectively, on 40 mg monthly octreotide – long – acting – repeatable in those who underwent hypophysectomy and by 63.5% and 38%, respectively, in those with no history of hypophysectomy. Those two biomarkers drop by 61.4% and 35.3% in those harboring macroadenoma and by 70% and 42% in those harboring microadenoma. The decrement of growth hormone, and insulin like growth factor-1 was found to be 70% and 41.9%, respectively, in those with disease duration ≥ 10 years and by 66.9% and 34.8% in those with disease duration < 10 years.

In males these biomarkers drop by 63% and 38% while in females, they drop by 59% and 31%, 6 months after doubling the dose of octreotide – long – acting – repeatable. No patient developed impairment of glucose tolerance or gall stones at the end of study period.

Conclusion: Increasing the dose of octreotide – long – acting – repeatable from 20 to 40 mg every 28 days in acromegalic patients, resistant to the conventional dose of octreotide – long – acting – repeatable is found to be fruitful in reducing growth hormone and insulin like growth factor-1 by significant percentage irrespective of gender, disease duration, previous hypophysectomy or harboring micro or macro adenoma.

Keywords: **Octreotide, Growth hormone, Insulin like growth factor-1, Glucose tolerance test, Acromegaly.**

Iraqi Medical Journal Vol. 64, No. 1, January 2018; p.56-63.

Acromegaly is known to reduce life expectancy. Predictors of survival are growth hormone (GH) ≤ 2.5 µg/L and normal Insulin like growth factor-1 (IGF-1)[(1)].

After a year of use of octreotide long – acting – repeatable (LAR) control of GH and IGF-1 is achieved in 54% and 63% of acromegaly patients, achievement of IGF-1 normalization increases with time[(2)].

*National Diabetes Center, Al-Mustansyria University

The usual doses of monthly octreotide is 10-20 mg but higher doses may be needed for resistant cases thus dose up titration may be fruitful to achieve GH and IGF-1 targets[3,4].

Octreotide LAR was found to induce tumor shrinkage by > 50% of tumor volume in 44% of patients after a year of analog use.

Dose increment may be good option in order to normalize GH and IGF-1[5].

The goal of treating acromegaly is to suppress GH, and IGF-1, inducing tumor shrinkage plus maintaining normal anterior pituitary function [6].

We have to keep in mind the importance of GH control as it was found to be the most important determinant of mortality[7].

Methods

Seventeen acromegalic patients, while on monthly injection of 20 mg long-acting octreotide (sandostatin LAR) who fail to achieve acceptable reduction of GH below 2.5 ng/ml and IGF-1 to that of their age and sex matched levels after one year of treatment despite their compliance with the drug. All are enrolled in a study to assess the achievement of increasing the dose from 20 mg to 40 mg of monthly injection of sandostatin LAR for 6 months.

Fourteen patients (82.36%) have pituitary macroadenoma (more than 10 mm in diameter) while the remaining three patients (17.64%) had microadenoma (less than 10 mm in diameter). The mean duration of the disease is less than 10 years in 9 patients (52.9%) and equal or more than 10 years in the remaining 8 patients (47.1%). Surgery (trans–sphenoidal hypophysectomy) was done for seven patients (41.1%) and 10 patients (58.9%) had no history of surgery. Eleven patients (64.7%) were males and six patients (35.3%) were females.

This group of patients was enrolled in the study and start to have double the dose from 20 mg to 40 mg of long-acting octreotide (Sandostatin LAR) monthly for 6 months; thus their GH and IGF-1 start to drop in different percentages. IGF-1 drops but really not reaching the target of normal age and sex matched level.

The GH and IGF-1 drop by a variable percentage according to the status whether harboring micro versus macroadenoma, having the disease for ≥ or < than 10 years, they had history of surgery or not and according to the gender. All the above-mentioned variables were taken in consideration.

All the recruited patients have no adverse events in the form of glucose intolerance or gall stones, while on 20 mg monthly octreotide (LAR).

Oral glucose tolerance test (OGTT) was conducted before and after dose escalation and no patient develop impaired fasting glucose (fasting plasma glucose 110-125 mg/dl) or impaired OGTT (postprandial glucose 140-199 mg/dl) ultrasound examination was done before and after dose escalation, no one developed gall stones.

Results

In patients who underwent surgery their baseline mean GH drops from 20.22 ng/ml to 7.57 ng/ml so the decrement was 12.65 ng/ml (62.5%). While the baseline mean IGF-1 in those patients was 953.1 ng/ml dropped to 599.7 ng/ml, thus it drops by 353 ng/dl (37%), (Table 1).

In patients who have no history of surgery the baseline mean GH was 20.46 ng/ml drops to 7.47 ng/ml so it drops by 12.99 ng/ml (63.5%). while the baseline mean IGF-1 was 959.3 ng/ml it drops to 591 ng/ml so the decrement was 367.8 ng/ml (38%), (Table 2).

The reduction of IGF-1 and GH in both groups of patients who have previous surgery compared to those who have no history of surgery is promising and have no significant difference for GH and IGF-1, respectively, (Figure 1).

For patients with macroadenma, the baseline mean GH drops from 20.83 ng/ml to 8.04 ng/ml so their decrement was 12.7 ng/ml (61.4%). while their baseline mean IGF-1 was 970 ng/ml drops to 627.2 ng/ml, thus their decrement is 342.8 ng/ml (35.3%), (Table 3).

For patients who are harboring pituitary microadenoma; their baseline mean GH levels was 20.25 ng/ml drops to 6.04 ng/ml, thus the reduction was 14.21 ng/ml (70%). while their baseline mean IGF-1 level was 937 ng/ml drops to 543.4 ng/ml, so the degree of reduction 393.6 (42%).

The reduction of IGF-1 and GH although numerically clear and represent an achievement but the difference between patients with macroadenoma versus microadenoma was not significant between the two groups for both IGF-1 and GH (P-value 0.3, 0.2, respectively), (Figure 2).

In patients with the mean duration of acromegaly of more than 10 years their baseline mean GH was 20.25 ng/ml drop to 6.04 ng/ml so the decrement was 14.21 ng/ml (70%). while the baseline mean IGF-1 was 936.7 ng/ml drops to 543.4 ng/ml so the decrement was 393.3 ng/ml (41.9%), (Table 5).

In patient with mean duration of acromegaly of less than 10 years the baseline mean GH was 21.08 ng/ml drops to 6.97 ng/ml, so the decrement was 14.11 ng/ml (66.9%). While the baseline mean IGF-1 was 952.9 ng/ml drops to 620.6 ng/ml and the decrement was 332.3 ng/ml (34.8%), (Table 6).

The duration of acromegaly was found to be not affect the achievement of reducing GH and IGF-1 by doubling the dose thus a duration of more than 10 years is not regarded as an obstacle against escalating the dose which reflect the non significant difference of GH and IGF-1 reduction in those who has the disease for more or less than 10 years duration, (Figure 3).

The baseline mean GH in male patients was 20.46 ng/ml drops to 7.47 ng/ml, thus the decrement was 12.99 ng/ml (63%). While the baseline mean IGF-1 was 959.3 ng/ml drops to 591.5 ng/ml thus the decrement was 367.8 ng/ml (38%), (Table 7).

The baseline mean GH in female was 21 ng/ml drops to 8.59 ng/ml. Therefore, the reduction was 12.41 ng/ml (59%). While the baseline mean IGF-1 in female was 982.9 ng/ml drops to 675.8 ng/ml so the degree of reduction was 307.1ng/ml (31%), (Table 8).

The percentage of reduction of GH, IGF-1 are evident in both genders after escalating the monthly dose and the difference between males and females found not to be significant (P-value 0.1, 0.4, respectively), (Figure 4).

Table 1: Reduction of GH, IGF-1 in acromegalic patients who underwent hypophysectomy by increasing the dose of LAR from 20 mg to 40 mg monthly.

Dose of monthly LAR	GH (ng/ml) M±SD	IGF1 (ng/ml) M±SD
20 mg	20.22 ± 2.36	953.1± 329.8
40 mg	7.57 ± 2.21	599.7 ± 314.2
Decrement	12.65	353.4
% of decrement	62.5%	37%
P-value	<0.05	<0.01
Level of significance	Significant	Highly significant

Table 2: Reduction of GH, IGF-1 in acromegalic patients who no history of hypophysectomy after increasing the dose of LAR from 20 mg to 40 mg monthly.

Dose of monthly LAR	GH (ng/ml) M±SD	IGF1 (ng/ml) M±SD
20 mg	20.46 ± 2.19	959.3 ± 325.2
40 mg	7.47 ± 2.23	591.5 ± 319.3
Decrement	12.99	367.8
% of decrement	63.5%	38%
P-value	<0.05	<0.01
Level of significance	Significant	Highly significant

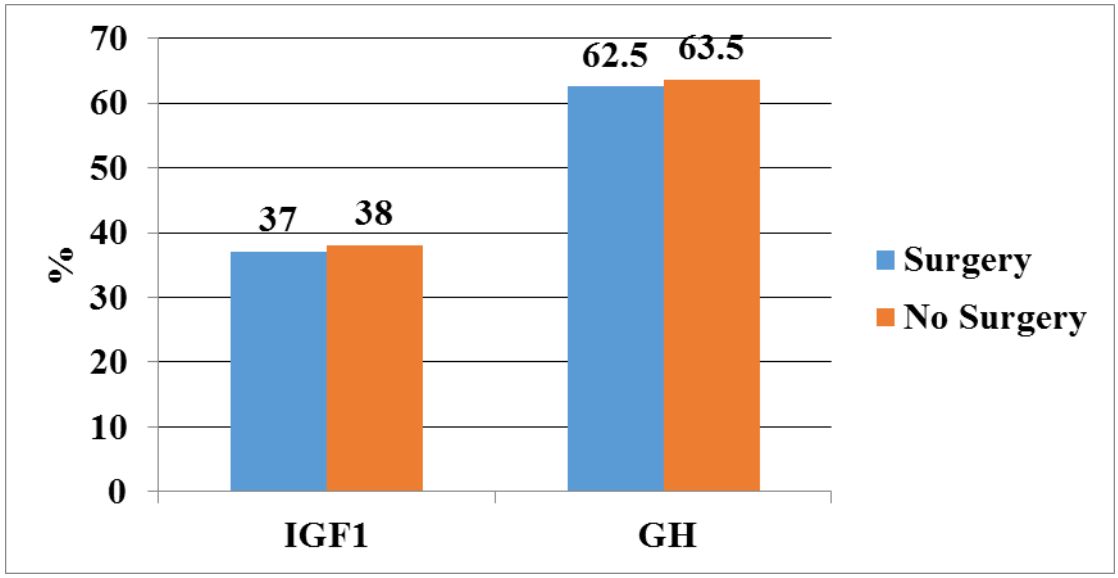

Figure 1: The percentage of IGF1, GH reduction after shifting from 20 to 40 mg long – acting octreotide (LAR) in patients with previous history of hypophysectomy versus acromegalic patients with no history of hypophysectomy.

Table 3: Reduction of GH, IGF-1 by doubling the monthly dose of LAR from 20 to 40 mg in acromegalic patients harboring pituitary macroadenoma.

Dose of monthly LAR	GH (ng/ml) M±SD	IGF1 (ng/ml) M±SD
20 mg	20.83 ± 3.01	970 ± 334.1
40 mg	8.04 ± 2.46	627 ± 304.6
Decrement	12.7	342.8
% of decrement	61.4%	35.3%
P-value	<0.05	<0.01
Level of significance	Significant	Highly significant

Table 4: Reduction of GH, IGF-1 by doubling the monthly dose of LAR from 20 to 40 mg in acromegalic patients harboring pituitary microadenoma.

Dose of monthly LAR	GH (ng/ml) M±SD	IGF1 (ng/ml) M±SD
20 mg	20.25 ± 2.5	936.7 ± 373.5
40 mg	6.04 ± 2.2	543.4 ± 322.5
Decrement	14.21	393.6
% of decrement	70%	42%
P-value	<0.05	<0.01
Level of significance	Significant	Highly significant

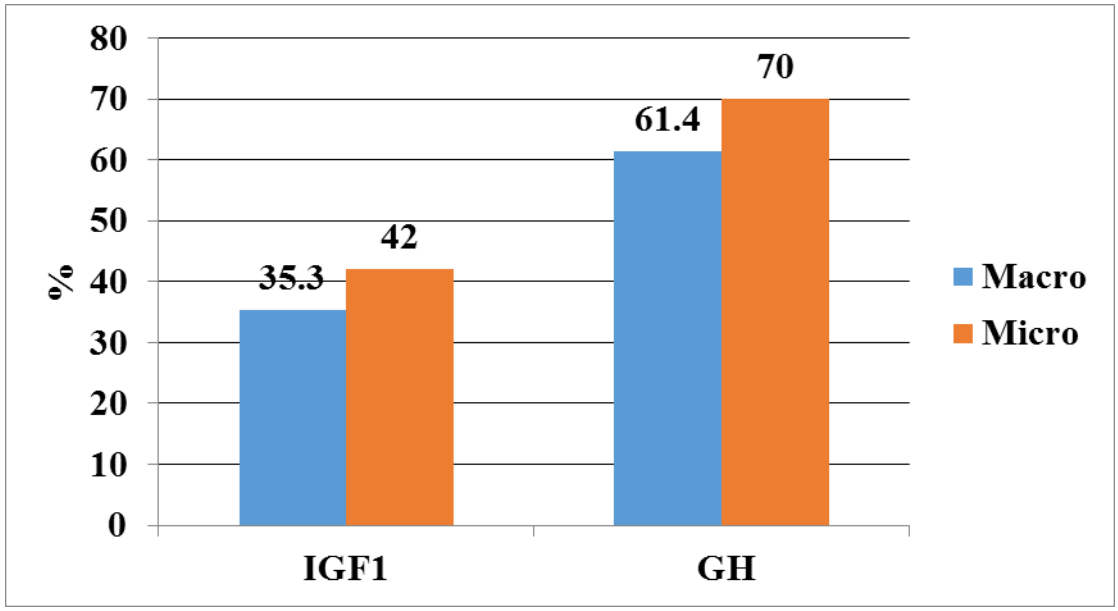

Figure 2: The percentage of IGF1, GH reduction after shifting from 20 to 40 mg LAR (long acting octreotide) in patients harboring GH secreting micro or macroadenoma.

Table 5: Reduction of GH, IGF-1 by doubling the monthly dose of LAR in acromegalic patients in whom the mean duration of the disease is more than 10 years.

Dose of monthly LAR	GH (ng/ml) M±SD	IGF1 (ng/ml) M±SD
20 mg	20.25 ± 2.5	936.7 ± 373.5
40 mg	6.04 ± 2.2	543.4 ± 322.5
Decrement	14.21	393.3
% of decrement	70%	41.9%
P-value	<0.05	<0.01
Level of significance	Significant	Highly significant

Table 6: Reduction of GH, IGF-1 by doubling the monthly dose of LAR in acromegalic patients in whom the mean duration of the disease is less than 10 years.

Dose of monthly LAR	GH (ng/ml) M±SD	IGF1 (ng/ml) M±SD
20 mg	21.08 ± 2.3	952.9 ± 282.1
40 mg	6.97 ± 3.2	620.6 ± 287.9
Decrement	14.11	332.3
% of decrement	66.9%	34.8%
P-value	<0.05	<0.01
Level of significance	Significant	Highly significant

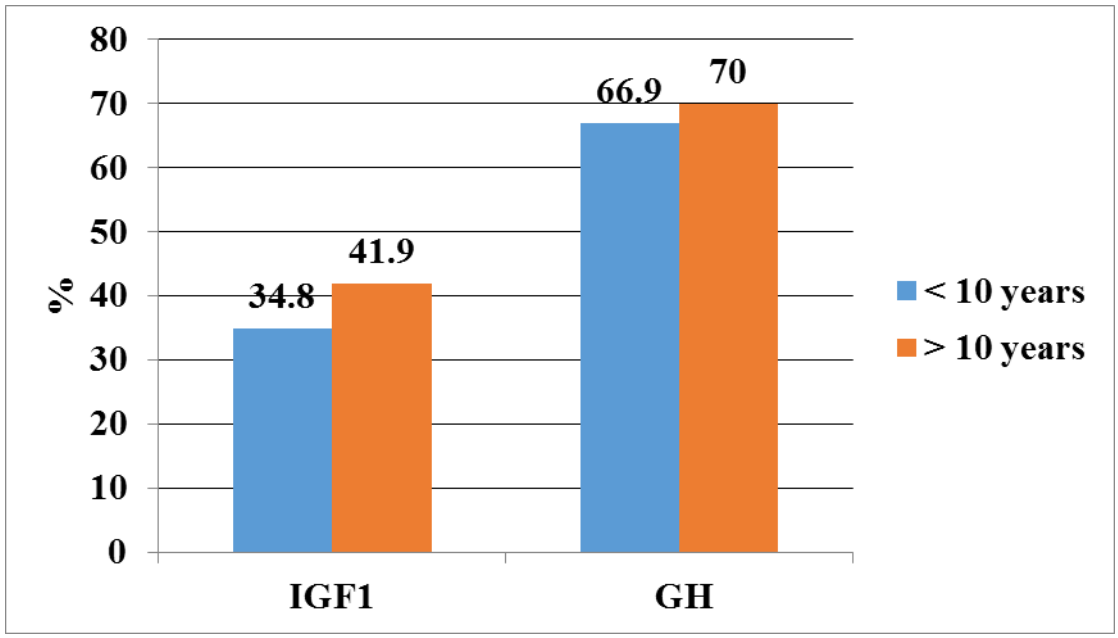

Figure 3: The percentage of IGF1, GH reduction after shifting from 20 to 40 mg LAR long- acting octreotide in acromegalic patients with a disease duration of less than 10 years versus those with a duration exceeding 10 years.

Table 7: Reduction of GH, IGF-1 after doubling the monthly dose of LAR in acromegalic males.

Dose of monthly LAR	GH (ng/ml) M±SD	IGF1 (ng/ml) M±SD
20 mg	20.46 ± 2.19	959.3 ± 325.2
40 mg	7.47 ± 2.23	591.5 ± 319.3
Decrement	12.99	367.8
% of decrement	63%	38%
P-value	<0.05	<0.01
Level of significance	Significant	Highly significant

Table 8: Reduction of GH, IGF-1 after doubling the dose of LAR in acromegalic females.

Dose of monthly LAR	GH (ng/ml) M±SD	IGF1 (ng/ml) M±SD
20 mg	21 ± 2.8	982.9 ± 347.7
40 mg	8.59 ± 1.7	675.8 ± 280.3
Decrement	12.41	307.1
% of decrement	59%	31%
P-value	<0.05	<0.01
Level of significance	Significant	Highly significant

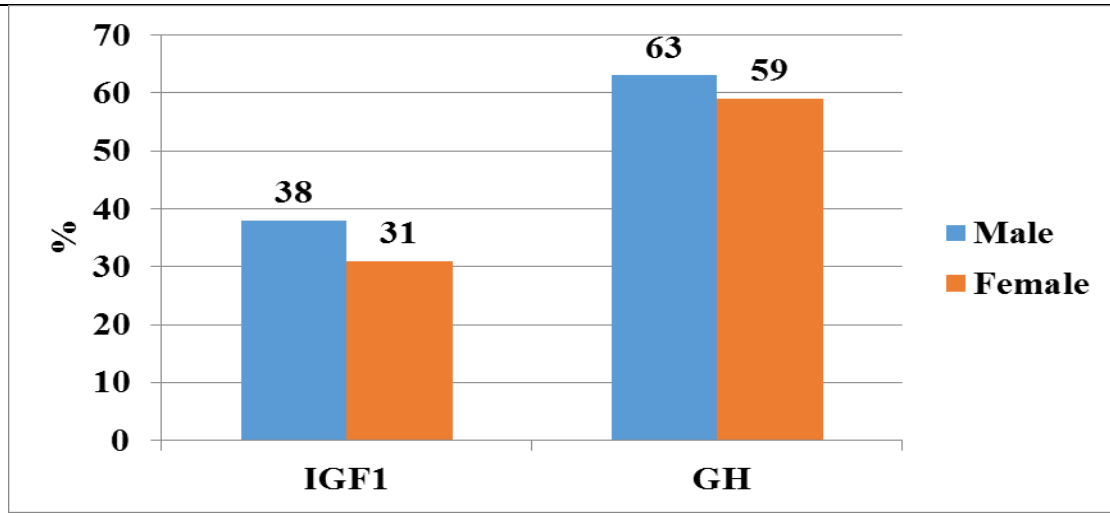

Figure 4: The percentage of IGF1, GH reduction after shifting from 20 to 40 mg LAR long- acting octreotide according to their gender.

Discussion

The current study shows that increasing LAR dose to 40 mg monthly results in fruitful decrement of the biomarkers which define control and cure of acromegalic patients.

The main target of treating acromegalic patients is to improve survival by reducing the level of GH to < 2 µg/L and IGF-1 to normal thus achieving the goal which is known to be associated with normal life expectancy[8].

According to the available guidelines, the gold standard treatment of acromegaly is trans-sphenoidal hypophysectomy (TSH) and or radiotherapy but surgical cure is achieved in 50% and radio therapy take around 10 years to lower GH to the target[9].

Octreotide LAR is known to cause nausea, bloating in 8% and gall stones or sludge in 18% as adverse events, however dose escalation is found not to increase the risk of these side effects and not to have a meaningful worsening of glucose tolerance[10].

The rational for dose optimization is the fact that, control of GH and IGF-1can lead to both reversal of comorbidities and reduction of mortality[11].

The reported proportion in whom there was reduction in GH level (<2.5 µg/L) and normalization of IGF-1 was 57% and 67%, respectively, following octreotide therapy, and 48% and 47%, respectively, following therapy with lanreotide depot[12].

Octreotide LAR was found to be equally effective in previously untreated acromegaly patients (primary treatment group) and previously treated with surgery or radiotherapy or both (secondary treatment group)[13].

IGF-1 is reduced to normal levels by octreotide LAR In 68% of primary treatment group and 62% of secondary treatment group while GH reached normal levels in 70% of primary treatment group and 61% of secondary treatment group[14].

Dose escalation provide improved efficacy without significant change in the recorded side effects and tolerability[15].

Upgrading the dose have been tried by pervious workers[16], most of the author's advocated gradual upgrading of the dose from 20 to 30 to 40 mg according to the patients status.

The dose of octreotide LAR is variable, ranging from 10-40 mg monthly, meta-

analysis of many studies, 53% of patients, require 30 mg, 60% required 20 mg to achieve the recommended goals[17]. Data on dose escalation of octreotide LAR as primary therapy of acromegaly (without hypophysectomy) are lacking.

In conclusion; This study shows that, octreotide – LAR dose escalation from 20 mg every 28 days to 40 mg every 28 days results in marked reduction of GH and IGF-I to good percentage without causing meaningful side effects as impaired glucose tolerance or development of gall-stones.

Octreotide – LAR dose up-titration may be useful for acromegalic patients irrespective to their gender, adenoma size, previous surgery and disease duration.

Further studies or recommended to enroll large number of acromegalic patients and for longer period of time, because of the scares data and rarity of the disease. This area of endocrinology may be fertile media for physician opinion and personalized medicine.

References

1- Melmed S. Medical progress Acromegaly. New England Journal of medicine 2006; 355: 2558-73.
2- Cozzi R, Montini M, Attanasio et al. Primary treatment of acromegaly with octreotide (LAR): perspective study of its efficacy in control of disease activity and tumor shrinkage. Journal of Clinical Endocrinology and Metabolism 2006; 91: 1397-403.
3- Turner HE, Vadivale A, Keenan J, Wass JA. A comparison of lanreotide and octreotide LAR for treatment of acromegaly. Clinical Journal Endocrinology 1999; 51: 275-80.
4- Colao A, Privonello R, Auriemma RS, Briganti E, Galdiero M, Tortora F, Caranci F, Cirillo S, Lombardi G. Predictors of tumor shrinkage after primary therapy with somatostatin analogues in acromegaly: A prospective study in 99 patients. Journal of Clinical Endocrinology and Metabolism 2006; 91: 2112-8.
5- Cozzi A, Attanasio R, Montini M, Pagani G, Lasio G, Lodrini S. Barausse M, Albizzi M, Dallabonzani D, Pedroncelli AM. Four – year treatment with octreotide –LAR in 110 acromegalic patients: the predictive value of short- term results by ROC analysis. Journal of Clinical Endocrinology and Metabolism 2003; 88; 3090-8.
6- Colao A, Ferone D, Marzullo P, Cappabiance P, Cirillo S, Boerlin V, Lancranjan I, Lombardi G. Long – term effect of depot long-acting somatostatin analog. Octreotide on hormone levels and tumor mass in acromegaly. Journal of Clinical Endocrinology and Metabolism 2001; 86: 2779-86.
7- Giustina A, Chanson P, Kleinberg D, et al. Expert consensus document a consensus on the medical treatment of acromegaly. Nat Rev Endocrinol 2014; 10: 243-8.
8- Holdaway IM, Rajasooryia RC, Gamble GD. Factors influencing mortality in acromegaly. J Clin Endocrinol Metab 2004; 89: 667-74.
9- Melmed S. Medical progress: acromegaly. New England Journal of Medicine 2006; 355: 2558-73.
10-Colar A, Ferone D, Marzullo P, et al. Systemic Complications of acromegaly Epidemiology, pathogenesis and management. Endocrine Reviews 2004; 25: 102-52.
11-Yetkin Do, Boysan SN, Tiryakiou O, et al. Forty – month follow up of persistent and difficulty controlled acromegalic patients treated with depot long-acting somatostatin analog octreotide. Endocr J 2007; 54: 512-9.
12-Ayuk J, Sheppard MC. Growth hormone and its disorders. Postgrad Med J 2006; 82: 24-30.
13-Fedra PU, Katzenelson L, Vandelely AJ, et al. Long – acting somatostatin analog therapy in acromegaly: A meta-analysis. J Clinic Metab 2005; 90: 4465-73.
14-Newmoh CB, Melmed S, George A et al. Octreotide as primary therapy for acromegaly. J Clinic Endocrinol Metab 1998; 83 (a): 3034-40.
15-Modlin IM, Latich I, Kidd M, Zikusoka M, Eick G. Therapeutic options for gastrointestinal characinoid. Clinic Gastroenterol Hepatol 2006; 4: 526-47.
16- Colao A, Pivonello R, Auriemma R, Galdiero M, Savastang S, Lombardi G. Beneficial effect of dose escalation of octreotide-LAR as first –line therapy in patients with acromegaly. Eur J Endocrinol 17(5): 579-87.
17- Annamaria AL Colao. Dose Escalation of Octreotide-LAR as First-Line Therapy in Resistant Acromegaly (HDacro) (clinical trial). Sponsor by Federico II University. Department of Molecular and Clinical Endocrinology and Oncology University Federico II of Naples. April 2007. Clinical Trials. govidentifier: NCT00461149. https://clinicaltrials.gov/ct2/show/study/NCT00461149