Octreotide-LAR as primary therapy for acromegaly: a retrospective serial case

Abstract

Acromegaly is a chronic disease. We evaluated 10 patients with acromegaly who were given octreotide LAR as primary treatment for acromegaly. In these patients, we observed a 25% and 60% decrease in the levels of Insulin-like Growth Factor-I (IGF-I) at 6 and 12 months, respectively, and IGF-I normalization rates of 25% and 30% for the same time points, respectively. Comparing the decrease in IGF-I after the treatment was instituted, a significant reduction was found at 6 months (p = 0.001) and at 12 months (p = 0.048). Response to therapy was dependent on tumor size and showed better results for microadenomas, with tumor shrinkage in 40%. The response to octreotide LAR therapy is satisfactory in patients with acromegaly, although it is still less effective than the results obtained with surgery. Nevertheless, octreotide LAR is an effective treatment option, particularly for patients who are clinically unable to undergo surgery.

Keywords: acromegaly, octreotide, somatostatin analogues, pituitary tumours, growth hormone

Introduction

Acromegaly is a chronic disease with signs and symptoms resulting from the excess of circulating growth hormone (GH). More than 95% of the cases are related to the presence of a GH-secreting adenoma. This hormone stimulates hepatic synthesis of the insulin-like growth factor type 1 (IGF-I), which is responsible for the GH-related somatic effects. The incidence of acromegaly is approximately 3-4 cases per million population, while prevalence is around 60 cases per million population per year. This condition occurs with equal frequency in males and females, more commonly in the fourth and fifth decades. Because of the insidious progression of acromegaly and failure to recognize its clinical manifestations, diagnosis is delayed in around 8 to 10 years after the onset of the disease. Continued exposure to excess GH and IGF-I is related to high morbidity and mortality due to cardiovascular, respiratory, neoplastic and metabolic complications, in addition to severe functional impairment as a result of skeletal complications. Recent evidence shows a mortality rate for acromegalic patients 1.7 times higher than that of the general population. The reverse proportion is true when GH levels are reduced to values below 2.5mcg/L, regardless of the therapy instituted. The treatment of acromegaly aims to reduce symptoms, control tumor growth, inhibit GH hypersecretion and normalize IGF-I serum concentrations, thereby reducing acromegaly-related morbidity and mortality. Three treatment options are available: surgery, drug therapy and radiotherapy. Transphenoidal surgery (TSS) is the first-line treatment for acromegaly, since the complete resection of the adenoma regulates hormone levels and improves the alterations that compromise tissues and organs. The success of TSS depends on the neurosurgeon’s experience and skills, the size and extension of the tumor and preoperative GH levels. In patients with a microadenoma, normalization of IGF-I occurs after TSS in 75-95% of the cases. Normalization is less frequent with macroadenomas, and is found in approximately 50% of cases. Medical treatment is often required, especially when no surgical cure is achieved and for patients at an advanced age and/or when severe comorbidity is present that contraindicates the surgery. Preoperative use of somatostatin analogs can be beneficial, as they promote tumor shrinkage and this facilitates surgical resection and attenuates the perioperative complications deriving from GH excess. The medical treatment options currently available are somatostatin analogs (octreotide, lanreotide (LAN) and pasireotide), dopamine agonists (bromocriptine and cabergoline), and GH-receptor antagonist pegvisomant. Somatostatin analogs lead to GH suppression in most acromegalic patients, with control of hormonal levels in approximately 60% of the patients. In addition, they induce tumor shrinkage in 30-50% of the acromegalic patients with GH levels below 20mcg/L when administered as primary therapy. Recent studies have shown tumor shrinkage of more than 20% of tumor volume in up to 100% of the patients treated with long-acting somatostatin analogs. The use of analogs was also successful in hormone regulation and volume reduction of residual tumor, with up to 80% of tumor shrinkage five years after the use of somatostatin analogs as primary treatment. Dopamine agonists also have their role in the treatment of acromegaly. In patients who achieve no control using somatostatin analogs, dopamine agonists are of help and provide further reduction in GH, IGF-I and tumor volume. Some other studies evaluated cabergoline as primary therapy; however, results were exceedingly discordant, ranging from 0% to 100% in the normalization of IGF-I. Cabergoline as a standalone treatment option shows only modest efficacy in acromegaly, with IGF-I decrease in around one third of the patients. Pegvisomant is the most recent pharmacological option for acromegaly. This drug limits the GH-induced hepatic synthesis of IGF-I, thereby reducing IGF-I levels by approximately 95%. The effect of pegvisomant is only peripheral, with no tumor volume alteration, which restricts its utility, especially for patients with a large residual tumor or those for whom medical treatment is considered the first-line therapy. Radiotherapy remains the third therapeutic option and is used less frequently. It is employed mostly for patients who obtained no disease control with surgery and medication. Among the medical treatment options available for acromegaly, somatostatin analogs are the class of drugs available for acromegaly, somatostatin analogs are the class of drugs available for acromegaly, somatostatin analogs are the class of drugs...
that promote the best results in controlling the disease and achieving tumor size reduction.

**Methods**

Ten patients whose primary treatment for acromegaly was pharmacological were assessed with regard to gender, age group, baseline IGF-I levels at 6 and 12 months of treatment and tumor size pre-treatment and at 6 months. All the patients had their IGF-I concentrations measured at 6 months of treatment, and eight of them were measured for IGF-I at 12 months of treatment. The objective of the treatment was IGF-I reduction or normalization. Treatment failure was considered in patients who did not achieve a decrease in IGF-I levels. The data were statistically analyzed using the SOFA software version 1.1.6. Parameters such as means and percent calculations were evaluated, and the t-test for matched variables was used.

**Results**

The demographics are given in Table 1. Most patients (2/3) were female and had macroadenomas. Two peaks of incidence were noted: in the fourth and seventh decade of life (Table 1). All patients showed elevated IGF-I levels for their age and gender. At 6 months, reduction in IGF-I levels occurred for 60% of the patients ($p<0.001$ vs. baseline). However, the decrease found in IGF-I concentrations at 6 months was not sustained at 12 months, when IGF-I reduction was 25% ($p=0.03$). Of the six patients whose IGF-I levels were lower at 6 months, four (66.7%) had elevated levels at 12 months. Regarding IGF-I normalization, we found 30% (3/10) of normal IGF-I levels at 6 months of treatment with LAR. At 12 months, the IGF-I normalization rate was 25% (2/8). The patients who showed normal IGF-I concentrations at 12 months had exhibited normalized levels already at 6 months (Tables 2) (Table 3). All the patients who showed normal IGF-I levels both at 6 and 12 months had microadenomas ($p<0.001$ vs. macroadenoma), were female and postmenopausal, with decreased estradiol levels.

**Table 1** Demographics of the acromegalic patients of the neuroendocrinology outpatient clinic at the Hospital Santa Marcelina who received primary therapy with LAR

| Gender | Age | Lesion size | Baseline IGF-I | IGF-I at 6 months | IGF-I at 12 months | Percentage of tumor reduction (%) |
|--------|-----|-------------|----------------|------------------|--------------------|----------------------------------|
| Female | 7   | micro       | 518            | 278              | 234                | -15                              |
| Female | 68  | micro       | 439            | 212              | 179                | -10                              |
| Female | 79  | micro       | 629            | 321              | 218                | -18                              |
| Male   | 34  | macro       | 718            | 652              | 559                | 0                                |
| Male   | 43  | macro       | 871            | 795              | 978                | 0                                |
| Male   | 74  | macro       | 654            | 458              | 524                | 10                               |
| Female | 53  | micro       | 412            | 257              | --                 | 0                                |
| Female | 46  | micro       | 382            | 225              | 189                | 0                                |
| Female | 71  | micro       | 517            | 202              | 167                | 0                                |
| Male   | 48  | macro       | 694            | 612              | --                 | 0                                |

However, if reduction/normalization of IGF-I levels are regarded as criteria of response to octreotide LAR, a marked response was noted at 6 months (90%), which was partially maintained at 12 months (50%) ($p=0.027$). Regarding tumor volume, magnetic resonance imaging (MRI) studies performed 6 months after the treatment with octreotide LAR revealed that tumor size was unchanged in 50% of the cases; 10% showed tumor growth, and 40% had reduced tumor size. Of the four patients who achieved tumor size reduction, three had microadenomas and IGF-I normalization, while one had a macroadenoma and achieved reduced, not normal, IGF-I levels (Table 4).

**Table 2** Profile of the acromegalic patients showing IGF-I levels observed during treatment; variations in tumor volume are also shown

| Patient | Gender | Age | Tumor size | Baseline IGF-I | IGF-I at 6 months | IGF-I at 12 months | Percentage of tumor reduction (%) |
|---------|--------|-----|------------|----------------|------------------|--------------------|----------------------------------|
| 1       | F      | 57  | micro      | 518            | 278              | 234                | -15                              |
| 2       | F      | 68  | micro      | 439            | 212              | 179                | -10                              |
| 3       | F      | 79  | micro      | 629            | 321              | 218                | -18                              |
| 4       | M      | 34  | macro      | 718            | 652              | 559                | 0                                |
| 5       | M      | 43  | macro      | 871            | 795              | 978                | 0                                |
| 6       | F      | 74  | macro      | 654            | 458              | 524                | 10                               |
| 7       | F      | 53  | micro      | 412            | 257              | --                 | 0                                |
| 8       | F      | 46  | micro      | 382            | 225              | 189                | 0                                |
| 9       | F      | 71  | micro      | 517            | 202              | 167                | 0                                |
| 10      | M      | 48  | macro      | 694            | 612              | --                 | 0                                |

**Table 3** Efficacy of primary therapy based on IGF-I levels after 6 and 12 months of treatment

| IGF-I | 6 months | % | 12 months | % |
|-------|----------|---|-----------|---|
| Reduction | 6  | 60 | 2  | 25 |
| Normalization | 3  | 30 | 2  | 25 |
| Failure | 1  | 10 | 4  | 50 |
| Total  | 10 | 100| 8  | 100|

*p<0.001 (baseline vs. 6 months)*

**p= 0.048 (baseline vs. 12 months)**

***p= 0.027 (6 months vs. 12 months)**
Conclusion

Octreotide LAR is effective in the treatment of acromegaly, as it shows significant results in terms of IGF-I reduction and normalization. However, the present results are still inferior to those observed with surgery; therefore, medical treatment should be indicated for patients who are not willing or able to undergo surgery or for cases in which surgery was not curative. Patients showing normalization of IGF-I at 6 months of treatment are more likely to maintain normal levels at 12 months. Tumor size influences the response to medical treatment, with microadenomas responding better both in the reduction of the IGF-I levels and in hormonal reduction. Presence of a microadenoma and normalization of IGF-I at 6 months of treatment with LAR are predictors of sustained biochemical control at 12 months of treatment. Patients who had their IGF-I levels reduced at 6 months-without normalization-are more likely to be unresponsive to medical treatment in 12 months.

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Conflict of interest

Author declares there is no conflict of interest.

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