PRACE ORYGINALNE/ORIGINAL PAPERS

The predictive value of the IGF-1 level in acromegaly patients treated by surgery and a somatostatin analogue

IGF-1 jako czynnik predykcyjny u pacjentów z akromegalią leczonych chirurgicznie i analogiem somatostatyny

Agata Bałdys-Waligórska, Anna Krzentowska-Korek, Filip Gołkowski, Grzegorz Sokołowski, Alicja Hubalewska-Dydejczyk

Department of Endocrinology, Jagiellonian University Medical College, Krakow, Poland

Abstract

Background: We evaluated the predictive value of IGF-1 against hGH in the treatment outcome.

Material and methods: A prospective study was undertaken of 47 patients (mean age 41.1 ± 12.9 years; 44 with macroadenoma and 3 with microadenoma), requiring treatment with octreotide LAR (SSLAR) following incomplete surgery. Concentrations of hGH and IGF-1 were measured three months after surgery and three, six, nine, 12, 18, and 24 months after introducing SSLAR.

Results: Following surgery, respective median values of hGH and IGF-1 concentrations were 5.55 ng/mL (IQR = 7.1) and 512.7 ng/mL (IQR = 379.5). After six, 12, and 24 months of SSLAR treatment, median values of hGH decreased significantly: to 2.95 ng/mL (IQR = 5.5, $p < 0.05$), 2.95 ng/mL (IQR = 4.4, $p < 0.05$) and 2.00 ng/mL (IQR = 3.6, $p < 0.001$), respectively.

After six, 12, and 24 months of SSLAR treatment, the respective median IGF-1 concentrations significantly decreased to 384.5 ng/mL (IQR = 312.2, $p < 0.01$), 323.0 ng/mL (IQR = 230.3, $p < 0.001$) and 334.0 ng/mL (IQR = 328.9, $p < 0.01$). The differences between median hGH and IGF-1 concentrations at 12 and 24 months were not significant. A statistically significant correlation was found between IGF-1 concentration prior to and after surgery (R = 0.61, $p < 0.05$) and prior to SSLAR treatment and IGF-1 concentration 24 months later (R = 0.49, $p < 0.05$). No such correlation was observed for hGH.

Conclusions: The level of IGF-1 prior to surgery and prior to SSLAR treatment is a better predictor of the treatment outcome than hGH. Octreotide LAR was most effective over the first 12 months of treatment. No further significant decrease of hGH or IGF-1 levels was observed past this period. **(Pol J Endocrinol 2011; 62 (5): 401–408)**

Key words: acromegaly, somatostatin analogues, octreotide, pituitary, growth hormone, insulin-like growth factor-1

Streszczenie

Wstęp: Porównano wartość predykcyjną stężenia IGF-1 oraz hGH w ocenie wyników leczenia akromegalii.

Materiał i metody: W prospektywnym badaniu wzięło udział 47 pacjentów (średnia wieku 41,1 ± 12,9 roku, 44 z makrogruczolakiem i 3 z mikrogruczolakiem przysadki), u których konieczne było zastosowanie leczenia oktreotydem LAR (SSLAR) po nieskutecznej operacji. Stężenia hGH i IGF-1 mierzono 3 miesiące po operacji oraz 3, 6, 9, 12, 18 i 24 miesiące po włączeniu leczenia SSLAR.

Wyniki: Stężenie hGH i IGF-1 po operacji wynosiło odpowiednio: 5,55 ng/mL (IQR = 7,1) i 512,7 ng/mL (IQR = 379,5).

Po 6, 12 i 24 miesiącach terapii SSLAR mediany stężenia hGH obniżyły się znamiennie do wartości odpowiednio: 2,95 ng/mL (IQR = 5,5, p < 0,05), 2,95 ng/mL (IQR = 4,4, p < 0,05) oraz 2,00 ng/mL (IQR = 3,6, p < 0,001). Po 6, 12 i 24 miesiącach leczenia SSLAR mediany stężenia IGF-1 obniżyły się znamiennie do wartości odpowiednio: 384,5 ng/mL (IQR = 312,2, p < 0,01), 323,0 ng/mL (IQR = 230,3, p < 0,001) oraz 334,0 ng/mL (IQR = 328,9, p < 0,01). Mediany stężenia hGH oraz IGF-1 po 12 i 24 miesiącach leczenia nie różniły się istotnie.

Stwierdzono znamienną korelację pomiędzy stężeniem IGF-1 przed operacją i po niej (R = 0,61, p < 0,05) oraz pomiędzy IGF-1 przed leczeniem SSLAR i po 24 miesiącach terapii (R = 0,49, p < 0,05). Nie obserwowano takiej zależności dla hGH.

Wnioski: Stężenie IGF-1 przed operacją i przed leczeniem SSLAR ma większą wartość predykcyjną wyniku leczenia niż stężenie hGH. Oktreotyd LAR był najskuteczniejszy w ciągu pierwszych 12 miesięcy terapii. Nie obserwowano dalszego znamiennego obniżenia stężenia hGH i IGF-1. **(Endokrynol Pol 2011; 62 (5): 401–408)**

Słowa kluczowe: akromegalia, analogi somatostatyny, oktreotyd, przysadka, hormon wzrostu, insulinopodobny czynnik wzrostu-1

Agata Bałdys-Waligórska, Katedra i Klinika Endokrynologii UJCM, ul. Kopernika 17, 31–501 Kraków, Poland,
tel.: +48 (12) 424 75 20, fax: +48 (12) 424 73 99, e-mail: awalig@cm-uj.krakow.pl

Introduction

The prevalence of acromegaly is generally estimated at 50–70 cases per million, while its incidence is about 3–4 cases per million inhabitants per year [1]. Thus, in Poland about 2,000 patients with acromegaly are to be expected. Due to slow tumour growth and insidious progression of the characteristic features of this disease, diagnosis may be delayed by up to ten years. The mortality of patients with uncontrolled acromegaly is considerably higher than that in normal populations, the standardised mortality ratio being 1.72 [2]. The life span of acromegaly patients is some ten years shorter than that of the general population [3]. The most common causes of death are cardiovascular, with 2–3 fold higher mortality than that of the general population [4–7]. Cerebrovascular [8, 9], respiratory and metabolic complications are also seen in these patients [10–13].

The prognostic factors which determine the course of acromegaly are permanently elevated concentrations of hGH (human growth hormone) and IGF-1 (insulin-like growth factor-1), patient age, size and invasiveness of tumour mass, as well as duration of symptoms and signs of disease [14].

Considering the relationship between hGH concentration and patient mortality, maintaining levels of hGH below 2.5 ng/mL in acromegaly patients resulted in their mortality approaching that of the general population [2, 4, 8]. Hence, this level for evaluating the outcome of surgery was approved at Cortina in the year 2000 [15]. However, Holdaway et al. [16] demonstrated that a better outcome could be achieved if levels of hGH < 1 ng/mL were maintained. This value was accepted in 2009 by the Acromegaly Consensus Group in Paris [17].

Treatment of acromegalic patients with somatostatin analogues decreases hGH and IGF-1 concentrations, improves their general and metabolic condition, and decreases morbidity and mortality. In postoperative follow-up, normalised IGF-1 concentration was strongly associated with lower prevalence of impaired glucose tolerance and lower diastolic blood pressure [18].

In our prospective uncontrolled and non-randomised study of the treatment outcome, we evaluated the predictive value of the level of IGF-1 prior to surgery and prior to octreotide LAR (SSLAR) treatment following incomplete surgery of pituitary adenoma, against the level of hGH.

Material and methods

We followed 85 acromegaly patients who underwent transsphenoidal surgery without SSLAR pre-treatment. Lack of such pre-treatment was due to limited availability of SSLAR in Poland in the early years of this study.

The presently applied standards of the Polish Endocrine Society, i.e. 6–12 months of treatment with somatostatin analogues (SSA) prior to surgery, were adopted in 2007 [19]. Of all 85 patients operated upon, 80% (68 patients) presented with macroadenoma and 20% (17 patients) with microadenoma. In all 85 patients the pituitary function was evaluated prior to and three months after surgery [20, 21]. Patients with impaired anterior pituitary function and/or diabetes insipidus received appropriate treatment. As based on the Cortina criteria [15], radical cure was achieved in 38 patients, i.e. in 44.7% of all patients operated upon. In the macroadenoma group, radical cure was achieved in 24/68 patients, i.e. in 35.3% of these patients operated, as compared to the microadenoma group in which 14/17 patients, i.e. 82.4%, were successfully operated.

A total of 47 patients (mean age 41.1 ± 12.9 years, 29 female and 18 male, 44 patients presenting with macroadenoma and 3 with microadenoma) required further treatment with SSLAR due to incomplete surgery. Three months after surgery, they had not fulfilled the cure criteria (basal hGH < 2.5 ng/ml, IGF-1 within normal range for age and sex and and no inhibition of hGH < 1.0 ng/mL in the 120th min of the OGTT). Eighteen patients who underwent pituitary surgery prior to the availability of somatostatin analogues in Poland in 2004 were re-evaluated before commencing their SSLAR treatment (13 patients were qualified). The mean time of active disease duration prior to diagnosis was 8.1 ± 6.1 years.

The efficacy of treatment was evaluated by measuring concentrations of fasting hGH and IGF-1 prior to SSLAR treatment and repeated three, six, nine, 12, 18 and 24 months later. The dose of Sandostatin LAR was 20 mg/month, increased to 30 mg/month if an unsatisfactory response was observed, or decreased to 10 mg/month if satisfactory biochemical control was achieved over at least three consecutive months.

Serum hGH concentrations were measured using the IRMA method (Immunotech) with a detection limit of 0.03 ng/mL (WHO IS 98/574). Serum IGF-1 concentrations were determined using RIA (DiaSource) with a detection limit of 3.4 ng/mL (NIBSC 1st IRR 87/518).

This study was approved by the Ethical Committee of the Jagiellonian University (approval 154/B/2005). Written informed consent was obtained from all patients on their admission to hospital to approve their diagnostic and treatment procedures, follow-up and to compile their medical data into a research database.

Statistical analysis

Data analysis was performed using Statistica version 9.0 software. The Shapiro-Wilk test was applied to analyse distributions of data. As the data was found

not to be normally distributed, non-parametric tests were applied. Two-tailed tests were used throughout. Median values and inter-quartile ranges (IQR) of hGH and IGF-1 concentrations are therefore given. For paired data the Wilcoxon rank sum test, and for unpaired data the Mann-Whitney U test, were applied. Fisher's exact test and ANOVA Friedman test were used to evaluate the efficacy of SSLAR treatment over the given time periods. In longitudinal studies, we assumed that the intermittent missing observations were random [22]. In all 47 patients, baseline values of hGH and IGF-1 prior to pituitary surgery and prior to SSLAR treatment were established. As the number of missing values at each time point differed across the observation, the available number of patients is given as the value of n, along with the value of p. P < 0.05 was considered to be statistically significant.

Results

In 47 patients (55.3% of all patients operated upon) who required further treatment with SSLAR, the median values of hGH before and after surgery were 24.23 ng/mL (IQR = 35.8) and 5.55 ng/mL (IQR = 7.1), respectively, the difference being statistically significant (p < 0.0001, n = 47) (Figure 1). Respective median values of IGF-1 before and after surgery were 1,018.0 ng/mL (IQR = 433.9) and 512.7 ng/mL (IQR = 379.5), (p < 0.001, n = 47) (Figure 1). Median values of hGH in the 120th min of the OGTT before and after surgery were 11.3 ng/mL (IQR = 33.3) and 3.6 ng/mL (IQR = 1.8) respectively, the difference being statistically significant, p < 0.05, n = 47.

No significant correlation was found between maximum tumour diameter (median value 18 mm; min = 9 mm, max = 60 mm) and hGH or IGF-1 concentrations prior to surgery (p > 0.05, n = 47), nor was any significant correlation found between maximum tumour diameter and hGH or IGF-1 levels after surgery (p > 0.05, n = 47).

A significant correlation was found between IGF-1 serum concentration before and after surgery (Spearman correlation coefficient R = 0.61, p < 0.05, n = 47). No such correlation was found (p > 0.05) with respect to serum concentration of hGH prior to and after surgery.

Based on ANOVA Friedman test, a significant decrease in hGH (p < 0.05, n = 26) and IGF-1 (p < 0.05, n = 25) concentrations was stated over the time of SSLAR treatment.

After six, 12, and 24 months of SSLAR treatment, median values of hGH decreased significantly, compared to hGH levels before SSLAR treatment: to 2.95 ng/mL (IQR = 5.5, p < 0.05, n = 32), 2.95 ng/mL (IQR = 4.4, p < 0.05, n = 32) and 2.00 ng/mL (IQR = 3.6, p < 0.001, n = 28), respectively, as based on Wilcoxon rank sum matched-pairs test (Figure 2). The differences between median hGH concentrations at 12 and 24 months were not statistically significant (p > 0.05, n = 28) (Figure 2). After 24 months of SSLAR treatment, the median hGH concentration value decreased by a factor of 2.8.

After six, 12, and 24 months of SSLAR treatment, respective median IGF-1 levels also significantly decreased as compared to those before SSLAR treatment: 384.5 ng/mL (IQR = 312.2, p < 0.01, n = 28), 323.0 ng/mL (IQR = 230.3, p < 0.001, n = 31) and 334.0 ng/mL (IQR = 328.9, p < 0.01, n = 28) (Figure 3). The
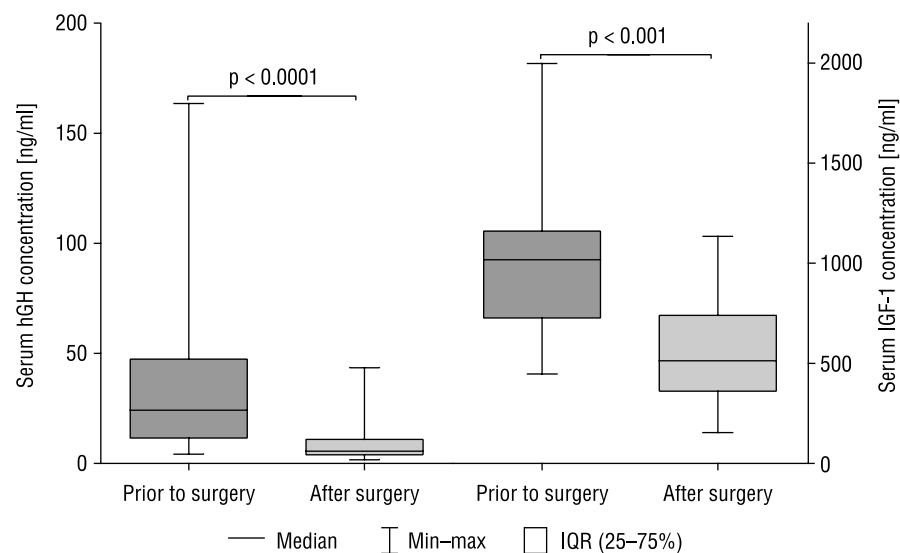

Figure 1. *Median values of hGH and IGF-1 concentration in acromegalic patients prior to and following unsuccessful surgery of pituitary adenoma (n = 47)*

Rycina 1. *Mediany stężenia hGH i IGF-1 przed i po nieskutecznej operacji gruczolaka przysadki u pacjentów z akromegalią (n = 47)*
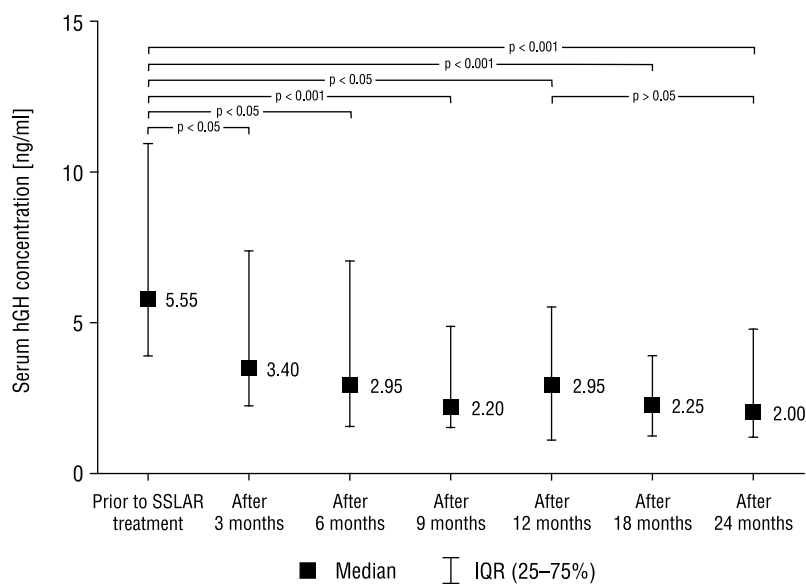
Figure 2. *Median values of hGH concentration in acromegalic patients treated with SSLAR following unsuccessful surgery — a 24 month observation (n = 47)*

Rycina 2. *Mediany stężenia hGH u pacjentów z akromegalią leczonych SSLAR po nieskutecznej operacji – obserwacja 24-miesięczna (n = 47)*
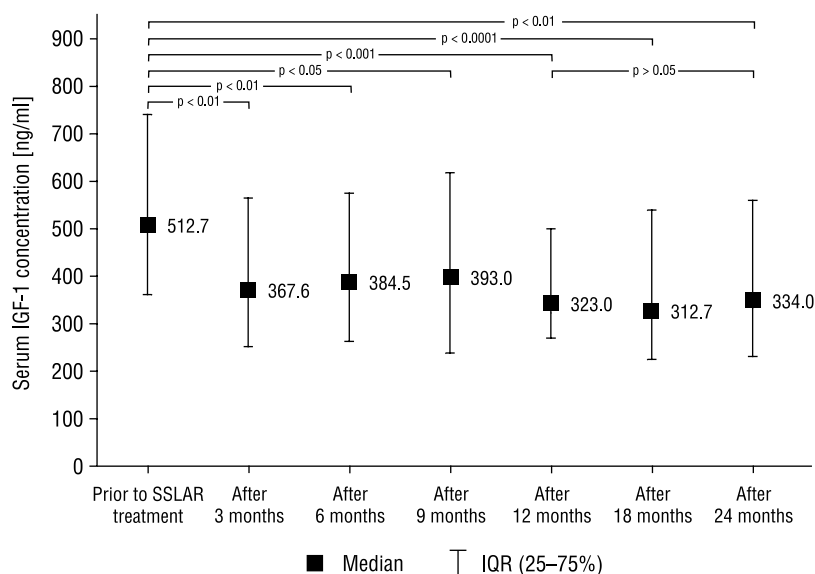

Figure 3. *Median values of IGF-1 concentration in acromegalic patients treated with SSLAR following unsuccessful surgery — a 24 month observation (n = 47)*

Rycina 3. *Mediany stężenia IGF-1 u pacjentów z akromegalią leczonych SSLAR po nieskutecznej operacji — obserwacja 24-miesięczna (n = 47)*

differences between median IGF-1 concentrations at 12 and 24 months were not significant ($p > 0.05$, n = 28) (Figure 3). After 24 months of SSLAR treatment, the median IGF-1 concentration value decreased by a factor of 1.5.

Prior to their SSLAR therapy, the median value of IGF-1 was 464.1 ng/mL (IQR = 289.4, n = 16) in the group of patients who achieved normal IGF-1 concentration after 24 months of treatment, and 744.0 ng/mL (IQR = 420.5, n = 11) in the group who did not, the difference being statistically significant (U Mann-Whitney test, $p < 0.05$) (Figure 4). The median values of hGH prior to SSLAR treatment in the group who achieved
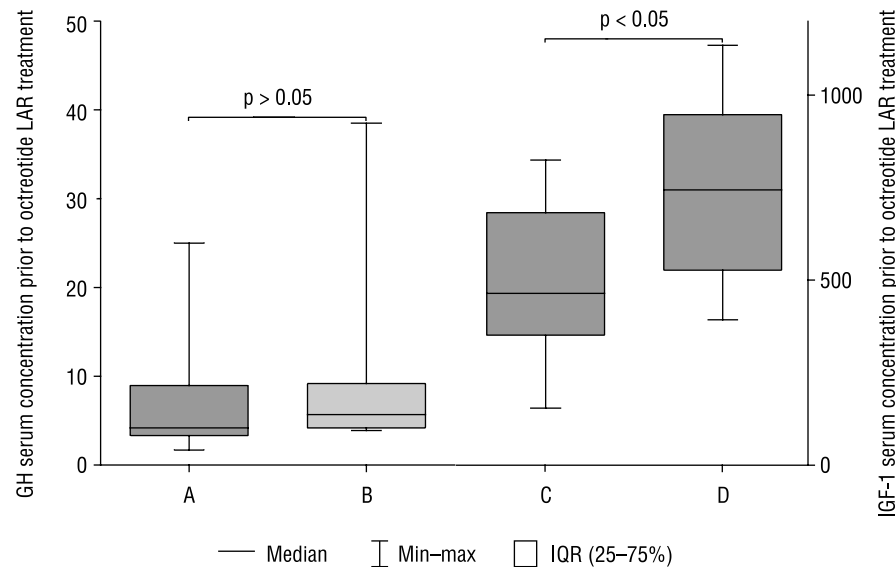
Figure 4. *Median values of hGH and IGF-1 concentrations in acromegalic patients prior to SSLAR treatment. A — patients who achieved the level of hGH < 2.5 ng/mL after 24 months of SSLAR treatment. B — patients with the level of hGH > 2.5 ng/mL after 24 months of SSLAR treatment. C — patients who achieved the level of IGF-1 within normal range for age and gender after 24 months of SSLAR treatment. D — patients with the level of IGF-1 above normal range for age and gender after 24 months of SSLAR treatment.*

Rycina 4. *Mediany stężenia hGH i IGF-1 u pacjentów z akromegalią przed leczeniem SSLAR. A — pacjenci, którzy osiągnęli stężenie hGH < 2,5 ng/mL po 24 miesiącach leczenia SSLAR. B — pacjenci, których stężenie hGH wynosiło > 2,5 ng/mL po 24 miesiącach leczenia SSLAR. C — pacjenci, którzy osiągnęli stężenie IGF-1 w normie dla wieku i płci po 24 miesiącach leczenia SSLAR. D — pacjenci ze stężeniem IGF-1 powyżej normy dla wieku i płci po 24 miesiącach leczenia SSLAR*

hGH < 2.5 ng/mL after 24 months of therapy and in the group who did not were 4.2 ng/mL (IQR = 5.5, n = 16) and 5.7 ng/mL (IQR = 5.0, n = 11), respectively ($p > 0.05$) (Figure 4).

Significant correlation was found between IGF-1 concentration before SSLAR treatment and IGF-1 concentration 24 months later, at the end of this observation (Spearman coefficient R = 0.49, $p < 0.05$, n = 28). No such correlation was observed for hGH after 24 months.

After six months of SSLAR treatment, hGH < 2.5 ng/mL and IGF-1 normalisation were achieved in 33.3% (10/30) and 42.3% (11/26) of patients, respectively. After 24 months of SSLAR treatment, hGH < 2.5 ng/mL and IGF-1 normalisation for age and gender were achieved in 60.7% (17/28) and 57.1% (16/28) of patients, respectively. After six and 24 months, normalisation of both parameters was achieved in 22.7% (5/22) and 40.0% (10/25) of patients, respectively (Figure 5). It also follows from Figure 5 that the percentage of patients who achieved normal IGF-1 after 12 months of treatment remained practically the same over the next 12 months of observation (54.8% *vs.* 57.1%), while the percentage of patients in whom hGH concentration did not exceed 2.5 ng/ml, increased (45.2% *vs.* 60.7%). However, based on exact Fisher test, these differences were not found to be statistically significant ($p > 0.05$).

Discussion

As active acromegaly typically remains undiagnosed for several years, the long-term effect of high concentrations of hGH and IGF-1 may result in the development of complications, such as cardiovascular [4–7], cerebrovascular [8, 9], respiratory or metabolic [10–13], or neoplastic [23]. Early diagnosis, cessation of hGH hypersecretion and normalisation of IGF-1 secretion are the main goals of acromegaly treatment, since biochemical control of the disease decreases morbidity and normalises the mortality rate in these patients [7, 16]. In our group of patients, the period of active disease was estimated at 8–14 years, with a high percentage of macroadenomas at the time of diagnosis, especially in patients with incomplete pituitary surgery (44/47 patients, 93.6%), compared to 70–73% in other studies [24–26].

While transsphenoidal selective tumour resection remains the treatment of choice [15, 27, 28], the efficacy of primary medical treatment using somatostatin analogues is currently under review [28–30]. For patients in whom surgery is unsuccessful, long-acting somatostatin analogues, presently octreotide or lanreotide, or pegvisomant, a hGH receptor antagonist, or combination treatments, are recommended [30–32]. The efficacy of surgery, which depends on the tumour size, on its location, and on
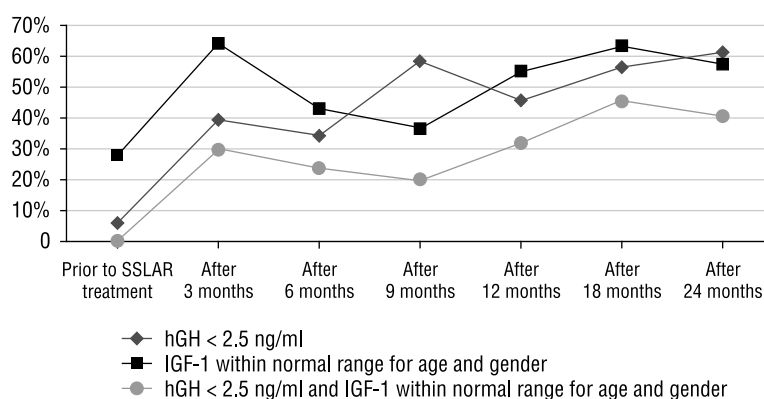
Figure 5. *Percentage of patients who achieved serum concentration of hGH < 2.5 ng/mL and IGF-1 concentration within normal range for age and gender in the course of SSLAR treatment following unsuccessful surgery (n = 47)*

Rycina 5. *Procent pacjentów, którzy osiągnęli stężenie hGH < 2,5 ng/mL i IGF-1 w normie dla wieku i płci w trakcie leczenia SSLAR po nieskutecznej operacji (n = 47)*

the baseline hGH level, is 61–91% in the case of microadenoma and 23–53% for macroadenoma [20, 21, 24, 33–35]. In our group of 85 patients who underwent surgery, cure was achieved in 35.3% of macroadenoma patients compared to 82.4% of microadenoma patients. Thus, in most of our patients, the disease persisted after surgery, requiring further treatment.

In the 47 patients in whom surgery was incomplete, no correlation was found between maximum tumour diameter and hGH or IGF-1 concentration prior to surgery, nor was any correlation found between maximum tumour diameter and hGH or IGF-1 concentration after surgery. Krzentowska-Korek et al. [20] found a correlation between basal serum hGH concentration and tumour size. Rieger et al. [36] reported that high hGH levels prior to and after surgery correlated better than IGF-1 with tumour size and invasiveness. Perhaps due to the high incidence of macroadenoma (over 90% of patients) with concomitant high serum hGH and IGF-1 concentrations, such a correlation was missing in our study. Under these circumstances, the efficacy of surgery, as based on hGH and IGF-1 concentration, is perhaps biased by tumour location, invasiveness, and the surgeon's experience [37].

While a positive correlation was found between IGF-1 concentration prior to and after surgery, no such correlation was found for hGH. Thus, in our study group, higher IGF-1 concentration prior to surgery indicated a poorer chance of acromegaly control by surgery alone. Indeed, Besser et al. [35] found several other predictors of acromegaly resistant to treatment i.e. large tumour size and high hGH secretion which were also present in our patients.

In our group of 47 acromegaly patients after incomplete pituitary adenoma surgery treated with SSLAR over

24 months, decreases in hGH and IGF-1 concentrations were observed. The median value of hGH concentration decreased from the initial 5.55 ng/mL to 2.0 ng/mL (a 64% decrease). After 24 months of treatment, the median value of IGF-1 concentration decreased from 512.7 ng/mL to 334.0 ng/mL (a 35% decrease).

We note consistency between our results and those of the retrospective study by Colao et al. [38]. In their study of the efficacy of postsurgical SSLAR treatment over a 12-month median observation time, a 40–80% decrease of hGH concentration depending on tumour size was observed, as was a 30–40% decrease of IGF-1 concentration from baseline over the same period. In a similar lanreotide post-surgery efficacy study, a decrease of 38% in mean hGH and IGF-1 concentrations from baseline values was found after 36 months of treatment [39].

In our group of patients, differences between the median concentrations of hGH or IGF-1 after 12 and 24 months of treatment were not significant. We therefore conclude that somatostatin analogues provide effective post-surgery therapy in acromegaly patients, and that the degree of disease control achievable within the first year of treatment is most important. While Maiza et al. [25] observed continuous decreases in hGH and IGF-1 over ten years of primary treatment with different SSA, Ayuk et al. [40] found no difference between hGH and IGF-1 concentrations after 24 and 48 weeks of Sandostatin LAR treatment in a group of 57 patients. We support the results of Ayuk et al. [40].

In the studied group of patients in whom surgery was not effective, we evaluated factors which could affect the efficacy of octreotide LAR treatment after 24 months. The baseline level of IGF-1 prior to SSLAR treatment was found to be an important indicator of the

final outcome of the 24-month treatment. Namely, in those patients in whom IGF-1 did not normalise for age and gender, the baseline level of IGF-1 was higher than that in patients in whom SSLAR was effective. No such relationship was observed with respect to the levels of hGH. Recently, Melmed et al. [41] have shown that less severe acromegaly at baseline can be controlled by low doses of lanreotide Autogel, although not all studies of somatostatin analogues agree with this observation [42]. While in our study, a positive correlation was found between IGF-1 concentration prior to SSLAR treatment and after 24 months, no such correlation was observed with respect to hGH. This suggests that the baseline level of IGF-1 may be more useful than hGH in predicting the outcome of SSLAR treatment. It would thus appear that IGF-1 is a more reliable marker, albeit not exclusively, in defining remission or cure [43]. Brabant et al. [44] demonstrated that serum concentration of IGF-1 correlates with clinical and biochemical features of acromegaly. It seems that IGF-1 is a more sensitive indicator of persistent disease activity than hGH [26, 43, 45], as the level of hGH is related to the remaining tumour mass, while the level of IGF-1 is related to the activity of hGH secreted by this mass.

Normalisation of both hGH and IGF-1 was achieved in 40% of our patients, in comparison with 38% achieved in a study of efficacy of lanreotide Autogel over 48 weeks by Chanson et al. [26] and with 43%, over 52 weeks, by Melmed et al. [41]. In a meta-analysis by Freda et al. [46], 56% and 66% of patients treated with SSLAR achieved cure criteria for hGH and IGF-1 respectively, although different observation periods were quoted and compared within this meta-analysis. In our study group, after 24 months of SSLAR treatment, levels of hGH < 2.5 ng/mL or IGF-1 normal for age and gender were achieved by 60.7% and 57.1% of patients, respectively. Calao et al. reported a decrease of hGH < 2.5 ng/mL in 56% of patients and normalised IGF-1 in 55% of their patients after a median 12 months of treatment [38]. In a recent randomised study of lanreotide Autogel, Melmed et al. [41] reported a decrease of hGH < 2.5 ng/mL in 54% of patients and normalised IGF-1 in 59% of patients after 52 weeks of treatment, as compared with our 45% and 55%, respectively, over the same period.

Conclusions

— We found the level of IGF-1 prior to surgery and prior to SSLAR treatment to be a better predictor of treatment outcome than the level of hGH.
— We found octreotide LAR to be most effective over the first 12 months of treatment. After that period, we have not observed any further significant decrease in hGH or IGF-1 levels up to two years of treatment.

Conflict of interest

Acknowledgements

References

1. Paisley A, Trainer PJ. Recent developments in the therapy of acromegaly. Expert Opin Investig Drugs 2006; 15: 251–256.
2. Dekkers OM, Biermasz NR, Pereira AM et al. Mortality in acromegaly: a meta–analysis. J Clin Endocrinol Metab 2008; 93: 61–67.
3. Rajasoorya C, Holdawey IM, Wrighston P et al. Determinant of clinical outcome and survival in acromegaly. Clin Endocrinol (Oxf) 1994; 42: 95–102.
4. Orme SM, McNally RJ, Cartwright RA et al. Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab 1998; 83: 2730–2734.
5. Kahaly G, Olshausen KV, Mohr-Kahaly S et al. Arrhythmia profile in acromegaly. Eur Heart J 1992; 13: 51–56.
6. Ozbey NC, Onccul A, Bugra Z et al. Acromegalic cardiomyopathy: evaluation of the left ventricular diastolic function in the subclinical stage. J Endocrinol Invest 1997; 20: 305–311.
7. Colao A. Improvement of cardiac parameters in patients with acromegaly treated with medical therapies. Pituitary DOI: 10.1007/s11102-011-0318-z
8. Ayuk J, Clayton RN, Holder G et al. Growth hormone and pituitary radiotherapy, but not serum insulin-like growth factor-1 concentrations, predict excess mortality in patients with acromegaly. J Clin Endocrinol Metab 2004; 89: 1613–1617.
9. Kauppinen-Mäkelin R, Sane T, Reunanen A et al. A nationwide survey of mortality in acromegaly. J Clin Endocrinol Metab 2005; 90: 4081–4086.
10. Weiss V, Sonka K, Pretl M et al. Prevalence of the sleep apnea syndrome in acromegaly population. J Endocrinol Invest 2000; 23: 515–519.
11. Herrmann BL, Severing M, Schmermund A et al. Impact of disease duration on coronary calcification in patients with acromegaly. Exp Clin Endocrinol Diabetes 2009; 117: 417–422.
12. Coculescu M, Niculescu D, Lichiardopol R et al. Insulin resistance and insulin secretion in non–diabetic acromegalic patients. Exp Clin Endocrinol Diabetes 2007; 115: 308–316.
13. Reincke M, Petersenn S, Buchfelder M et al. The German Acromegaly Registry: description of the database and initial results. E Exp Clin Endocrinol Diabetes 2006; 114: 498–505.
14. Melmed S. Medical progress: acromegaly. N Engl J Med 2006; 355: 2558–2573.
15. Giustina A, Barkan A, Casanueva F et al. Criteria for cure of acromegaly: a consensus statement. J Clin Endocrinol Metab 2000; 85: 526–529.
16. Holdaway IM, Rajasoorya RC, Gamble GD. Factors influencing mortality in acromegaly. J Clin Endocrinol Metab 2004; 89; 667–674.
17. Melmed S, Colao A, Barkan A et al. Acromegaly Consensus Group Guidelines for acromegaly management: an update. J Clin Endocrinol Metab 2009; 94: 1509–1517.
18. Serri O, Beauregard C, Hardy J. Long-term Biochemical status and disease-related morbidity in 53 postoperative patients with acromegaly. J Clin Endocrinol Metab 2004; 89: 658–661.
19. Bolanowski M, Bar-Andziak E, Kos-Kudła B et al. Konsensus Polskiego Towarzystwa Endokrynologicznego. Przygotowanie analogami somatostatyny do leczenia operacyjnego akromegalii (Somatostatin anlogue treatment in acromegaly — Consensus of the Polish Society of Endocrinology). Endokrynol Pol (Pol J Endocrinol) 2007; 58: 350–353.
20. Krzentowska-Korek A, Gołkowski F, Bałdys-Waligórska A et al. Efficacy and complications of neurosurgical treatment of acromegaly. Pituitary 2011; 14: 157–162.
21. Feelders RA, Bidlingmaier M, Strasburger CJ et al. Postoperative evaluation of patients with acromegaly: clinical significance and timing of oral glucose tolerance testing and measurement of (free) Insulin-like Growth Factor-1, Acid-labile Subunit, and Growth Hormone-binding Protein levels. J Clin Endocrinol Metab 2005; 90: 6480–6489.
22. Hedeker D, Gibbons RD. Application of random-effects pattern-mixture models for missing data in longitudinal studies. Psychological Methods 1997; 2: 64–78.
23. Bałdys-Waligórska A, Krzentowska A, Gołkowski F, Sokołowski G, Hubalewska-Dydejczyk A. The prevalence of benign and malignant neoplasms in acromegalic patients. Endokrynol Pol (Pol J Endocrinol) 2010; 61: 29–34.

PRACE ORYGINALNE

24. Baumann G. Acromegaly. Endocrinol Metab Clin North Am 1987; 16: 685–703.
25. Maiza JC, Vezzosi D, Matta M et al. Long term (up to 18 years) effects on GH/IGF-1 hypersecretion and tumour size of primary somatostatin analogue (SSTa) therapy in patients with GH-secreting pituitary adenoma responsive to SSTa. Clin Endocrinol (Oxf) 2007; 67: 282–289.
26. Chanson P, Borson-Chazot F, Kuhn JM et al. Lanreotide Acromegaly Study Group, Control of IGF-1 levels with titrated dosing of lanreotide Autogel over 48 weeks in patients with acromegaly. Clin Endocrinol (Oxf) 2008; 69: 299–305.
27. Lüdecke DK, Abe T. Transsphenoidal microsurgery for newly diagnosed acromegaly: a personal view after more than 1,000 operations. Neuroendocrinology 2006; 83: 230–239.
28. Melmed S, Casanueva FF, Cavagnini F et al. Acromegaly Treatment Consensus Workshop Participants, Guidelines for acromegaly management. J Clin Endocrinol Metab 2002; 87: 4054–4058.
29. Luque-Ramírez M, Portoles GR, Varela C et al. Spanish Multicentre Group for the Study of Acromegaly. The efficacy of octreotide LAR as first line therapy for patients with newly diagnosed acromegaly is independent of tumor extention: predictive factors of tumor and biochemical response. Horm Metab Res 2010; 42: 38–44.
30. Feelders RA, Hofland LJ, van Aken MO et al. Medical therapy of acromegaly: efficacy and safety of somatostatin analogues. Drugs 2009; 69: 2207–2226.
31. Debono M, Newell-Price J. New formulations and approaches in medical treatment of acromegaly. Current Opinion in Endocrinology. Curr Opin Endocrinol Diabetes Obes 2010; 17: 350–355.
32. Del Porto LA, Liubinas SV, Kaye AH. Treatment of persistent and recurrent acromegaly. J Clin Neurosci 2011; 18: 181–190.
33. Freda PU, Wardlaw SL, Post KD. Long-term endocrinological follow-up evaluation in 115 patients who underwent transsphenoidal surgery for acromegaly. J Neurosurg 1998; 89: 353–358.
34. Nomikos P, Buchfelder M, Fahlbush R. The outcome of surgery in 668 patients with acromegaly using current criteria of biochemical "cure". Eur J Endocrinol 2005; 152: 379–387.
35. Besser G, Burman P, Daly A. Predictors and rates of treatment-resistant tumour growth in acromegaly. Eur J Endocrinol 2005; 153: 187–193.
36. Rieger A, Rainov NG, Ebel H et al. Factors predicting pituitary adenoma invasiveness in acromegalic patients. Neurosurg Rev 1997; 20; 182–187.
37. Ahmed S, Elsheikh M, Stratton IM et al. Outcome of transsphenoidal surgery for acromegaly and its relationship to surgical experience. Clin Endocrinol (Oxf) 1999; 50; 561–567.
38. Colao A, Attanasio R, Pivonello R et al. Partial surgical removal of growth hormone–secreting pituitary tumors enhances the response to somatostatin analogs in acromegaly. J Clin Endocrinol Metab 2006; 91: 85–92.
39. Toledano Y, Rot L, Greenman Y et al. Efficacy of long-term lanreotide treatment in patients with acromegaly. Pituitary 2009; 12: 285–293.
40. Ayuk J, Stewart SE, Stewart PM et al. and the European Sandostatin LAR Group. Efficacy of sandostatin LAR (long-acting somatostatin analogue) is similar in patients with untreated acromegaly and in those previously treated with surgery and/or radiotherapy. Clin Endocrinol (Oxf) 2004; 60: 375–381.
41. Melmed S, Cook D, Schopohl J et al. Rapid and sustained reduction of serum growth hormone and insulin-like growth factor-1 with acromegaly receiving lanreotide Autogel therapy: a randomized, placebo-controlled, multicenter study with a 52 week open extension. Pituitary 2010; 13: 18–28.
42. Cozzi R, Montini M, Attanasio R et al. Primary treatment of acromegaly with octreotide LAR: a long-term (up to nine years) prospective study of its efficacy in the control of disease activity and tumor shrinkage. J Clin Endocrinol Metab 2006; 91: 1397–1403.
43. Brooke MA, Drake WM. Serum IGF-1 levels in diagnosis and monitoring of acromegaly. Pituitary 2007; 10: 173–179.
44. Brabant G. Insulin-like growth factor-1: marker for diagnosis of acromegaly and monitoring the efficacy of treatment. Eur J Endocrinol 2003; 148: 15–20.
45. Dimaraki EV, Jaffem CA, DeMott-Friberg R et al. Acromegaly with apparently normal GH secretion: implications for diagnosis and follow-up. J Clin Endocrinol Metab 2002; 87: 3537–3542.
46. Freda PU, Katznelson L, van der Lely AJ et al. Long acting somatostatin analog therapy of acromegaly: a meta-analysis. J Clin Endocrinol Metab 2005; 90: 4465–4473.