Endokrynologia Polska
DOI: 10.5603/EP.a2020.0050
Volume/Tom 71; Number/Numer 4/2020
ISSN 0423–104X

# Therapeutic effect of presurgical treatment with long-acting octreotide (Sandostatin® LAR®) in patients with acromegaly

*Marek Bolanowski[1], Wojciech Zgliczyński[2], Jerzy Sowiński[3], Agata Bałdys-Waligórska[4, 5], Grażyna Bednarek-Tupikowska[1], Przemysław Witek[2, 6], Grzegorz Zieliński[7], Włodzimierz Liebert[8], Lucyna Siemińska[9], Elżbieta Andrysiak-Mamos[10], Bogdan Marek[9, 11], Dariusz Kajdaniuk[9, 11], Joanna Malicka[12], Violetta Rosiek[9, 13], Aleksandra Jawiarczyk-Przybyłowska[1] and CSMS995BPL03 investigators*

[1]*Department of Endocrinology, Diabetes, and Isotope Therapy, Wrocław Medical University, Wroclaw, Poland*
[2]*Department of Endocrinology, Medical Centre Postgraduate Education, Warszawa, Poland*
[3]*Department of Endocrinology, Metabolism, and Internal Medicine, University of Medical Sciences, Poznan, Poland*
[4]*Department of Endocrinology and Internal Medicine, Andrzej Frycz Modrzewski Krakow University, Krakow, Poland*
[5]*Department of Endocrinology, Jagiellonian University, Kraków, Poland*
[6]*Department of Internal Medicine, Endocrinology, and Diabetes, Medical University of Warsaw, Warsaw, Poland*
[7]*Department of Neurosurgery, Military Medical Institute, Warsaw, Poland*
[8]*Department of Neurosurgery and Neurotraumatology, University of Medical Sciences, Poznan, Poland*
[9]*Department of Pathophysiology and Endocrinology, Medical University of Silesia, Katowice, Poland*
[10]*Department of Endocrinology, Pomeranian Medical University, Szczecin, Poland*
[11]*Department of Endocrinology and Metabolic Diseases, Regional Hospital, Rybnik, Poland*
[12]*Department of Endocrinology, Medical University, Lublin, Poland*
[13]*Department of Endocrinology and Neuroendocrine Tumours, Medical University of Silesia, Katowice, Poland*

## Abstract

**Introduction:** The aim of this study was to assess the therapeutic effect and the safety of pre-surgical treatment with long-acting octreotide in patients with acromegaly.

**Material and methods:** This project was conducted in 25 centres across Poland as a non-interventional, multicentre, observational study in patients with acromegaly, in which long-acting octreotide (Sandostatin® LAR®) was administered before surgery. They were 148 patients included into the study: 88 females and 60 males aged 18–86 years (51.3 ± 13.4).

**Results:** Eighty patients completed the study (underwent tumour surgery). The CRF included: baseline visit, four follow-up visits every three months before surgery, and two follow-up visits every three months after surgery. Sandostatin® LAR® was administered every four weeks. The efficacy measures were as follows: change of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) levels, number of patients fulfilling criteria of cure, and change of adenoma (micro- and macroadenomas) size during the treatment. Normalisation of GH and IGF-1 concentrations were obtained in 42.4 and 49.1% of patients at the end of medical therapy, respectively. Normalisation of GH and IGF-1 concentrations were obtained in 77.9 and 83.8% of patients after surgery, respectively. Reduction of microadenoma size was documented in 58.8% of patients, and in 70% of patients with macroadenomas at the end of medical therapy. In 74.0% of patients no pituitary tumour was shown on MRI after surgery.

**Conclusion:** In conclusion, we have shown good surgical outcome in patients with acromegaly after pre-treatment with somatostatin analogue, and good tolerance and safety of the therapy, supporting the national recommendation for pre-surgical treatment with long-acting somatostatin analogues in acromegaly patients. **(Endokrynol Pol 2020; 71 (4): 285–291)**

**Key words:** *acromegaly; presurgical pharmacotherapy; neurosurgery*

## Introduction

Acromegaly is a rare disease usually caused by growth hormone (GH)-secreting anterior pituitary adenoma. Typical clinical symptoms of the disease are accompanied by metabolic disturbances such as pre-diabetes or overt diabetes, hypertension, heart failure, neoplasms, and musculoskeletal disorders. These result in the increased mortality of patients with uncontrolled acromegaly [1, 2]. The aim of the treatment of acromegaly patients is normalisation of GH and insulin-like growth factor 1 (IGF-1) secretion, which restores life expectancy, decreases the frequency of complications, normalises metabolic disturbances, and improves quality of life. The radical method of treatment of acromegaly is selective transsphenoidal adenomectomy with the preser-

Prof. Marek Bolanowski, MD, PhD, Department of Endocrinology, Diabetes and Isotope Therapy, Medical University Wroclaw, Wybrzeże L. Pasteura 4, 50–367 Wrocław, Poland; e-mail: marek.bolanowski@umed.wroc.pl

vation of normal hormonal activity of the pituitary, if possible. The success rate of neurosurgical treatment depends on tumour size, location within the pituitary, and baseline GH concentration — reaching 61–91% in microadenomas and 23–53% in macroadenomas [3, 4]. Considering that in 70% of patients the tumour is macroadenoma, surgical treatment is not curative in the majority of cases. Therefore, medical therapy including long-acting somatostatin analogues (SSA) plays an important role in the treatment of acromegaly. They can be administered before surgery, used in the long-term treatment after unsuccessful surgery, or in cases when surgery is impossible (contraindications, patients refusing surgery). The treatment with SSA in acromegaly leads to normalisation of GH secretion in 50–60% of patients, normalisation of IGF-1 in 60–70%, shrinking of tumour size in 20–80%, and decreased metabolic disturbances and decreased risk of death [5, 6].

Several studies document the advantageous effects of pre-surgical SSA administration in acromegaly [7–9], but others do not support this attitude [10–12]. Recently performed meta-analyses deliver conflicting data [13–16]. Some guidelines advise [5] presurgical SSA application, whereas other do not [3, 4].

The aim of the study was to assess the therapeutic effect of pre-surgical treatment with long-acting octreotide formulation in patients with acromegaly, with separate consideration of pituitary micro- and macroadenomas, following the recommendations of the Polish Society of Endocrinology for the use of somatostatin analogues before surgery [5, 17].

## Material and methods

### *Study population*

The studied population comprised patients with documented acromegaly, who were candidates for treatment with SSA before the planned surgery. The assignment of patients to the treatment was not decided in advance by a trial protocol but was made under independent physician's decision and followed within the current practice of the participating centre. The inclusion criteria were as follows: age at least 18 years, confirmed diagnosis of acromegaly, and planned pituitary tumour surgery. During the years 2008–2012 a total of 148 patients with acromegaly were included into observation within this trial: 88 females and 60 males, 18–86 years of age (51.3 ± 13.4). Female patients were 53.6 ± 12.4 (18-86) and male patients were 48.1 ± 14.0 (19–79) years old, respectively.

A total of 80 patients completed the study (i.e. underwent transsphenoidal tumour surgery). They were 50 women and 30 men, with mean age 50.8 ± 11.2 years, mean duration of the disease 6.3 ± 5.3 years, harbouring microadenoma in 21 cases and macroadenoma in 59 ones. At baseline (initial visit) their mean GH level was 19.6 ± 21.0 ng/mL, and IGF-1 level was 789 ± 406 ng/mL.

Prior to enrolment in the study, previous surgical treatment was performed in 29 (19.6%) out of 148 patients, SSAs were administered to 44 patients (29.7%), dopamine agonists to 16 patients (10.8%), and SSA together with dopamine agonist to 12 (8.1%). In no patient previous radiotherapy was applied. The decision on concomitant medications, medicine prescription, or supportive care was taken by the treating physician in accordance with the current clinical practice of the participating centre. Characteristics of the study subjects is given in Table 1, their clinical symptoms severity in Table 2, and concomitant diseases in Table 3.

**Table 1.** *Age and sex structure of the 148 patients with acromegaly at the time of inclusion into the study*

| Age (years) | Women (n = 88) | Men (n = 60) |
|---|---|---|
| | (%) | (%) |
| Below 20 | 1 (1.1%) | 1 (1.7%) |
| 20–30 | 1 (1.1%) | 7 (11.7%) |
| 30–40 | 11 (12.5%) | 11 (18.3%) |
| 40–50 | 19 (21.7%) | 13 (21.7%) |
| 50–60 | 34 (38.7%) | 15 (25.0%) |
| 60–70 | 16 (18.1%) | 11 (18.3%) |
| 70–80 | 5 (5.7%) | 2 (3.3%) |
| Above 80 | 1 (1.1%) | 0 (0.0%) |

### *Methods*

This project was conducted in 25 centres across Poland in the form of a non-interventional, multicentre, observational post-marketing surveillance study in patients with documented acromegaly, in whom treatment with Sandostatin® LAR® was administered before surgery (CSMS995BPL03). Analysis concerned assessment

**Table 2.** *Main clinical symptoms related to acromegaly regarding their severity in the group of 148 patients with acromegaly*

| Symptoms reported | Severity of the symptom reported | | | | |
|---|---|---|---|---|---|
| | Very strong | Strong | Moderate | Mild | Absent |
| | (%) | (%) | (%) | (%) | (%) |
| Headache | 11 (7.4%) | 30 (20.4%) | 63 (42.6%) | 28 (18.9%) | 16 (10.8%) |
| Sweating | 16 (10.8%) | 53 (35.8%) | 48 (32.4%) | 21 (14.2%) | 9 (6.1%) |
| Swelling | 3 (2.0%) | 22 (14.9%) | 51 (34.5%) | 34 (23.0%) | 38 (25.7%) |
| Musculoskeletal pain | 5 (3.4%) | 46 (31.1%) | 63 (42.6%) | 17 (11.5%) | 17 (11.5%) |
| Constipation | 1 (0.7%) | 15 (10.1%) | 41 (27.7%) | 39 (26.4%) | 52 (35.1%) |
| Dyspnoea | 0 | 5 (3.4%) | 23 (15.5%) | 38 (25.7%) | 81 (54.7%) |
| Snoring | 11 (7.4%) | 35 (23.7%) | 32 (21.6%) | 43 (29.0%) | 27 (18.2%) |

**Table 3.** *Concomitant diseases in the group of 148 patients with acromegaly*

| Disease | Total (n = 148) | Women (n = 88) | Men (n = 60) |
|---|---|---|---|
| | (%) | (%) | (%) |
| Hypopituitarism | 28 (19%) | 19 (22%) | 9 (15%) |
| Diabetes mellitus | 37 (25%) | 26 (30%) | 11 (18%) |
| Glucose intolerance | 43 (29%) | 24 (27%) | 19 (32%) |
| Arterial hypertension | 83 (56%) | 46 (52%) | 37 (62%) |
| Goitre | 97 (66%) | 60 (68%) | 37 (62%) |
| Heart failure | 17 (11%) | 12 (14%) | 5 (8%) |
| Sleep apnoea | 20 (14%) | 11 (13%) | 9 (15%) |
| Colorectal cancer | 4 (3%) | 1 (1%) | 3 (5%) |
| Colon polyps | 9 (6%) | 5 (6%) | 4 (7%) |
| MEN | 2 (1%) | 0 | 2 (3%) |
| Primary hyperparathyroidism | 3 (2%) | 2 (2%) | 1 (2%) |
| Neuroendocrine tumours | 2 (1%) | 2 (2%) | 0 |
| Adrenal tumours | 4 (3%) | 3 (3%) | 1 (2%) |
| Amenorrhoea/impotence | 16 (11%) | 10 (11%) | 6 (10%) |

MEN — multiple endocrine neoplasia



methods and parameters used in routine clinical practice. Assessments were performed during each routine visit when medication was administered. During these visits data on the tolerability and safety of therapy were collected. Data were recorded in case report forms (CRF) in the form of "visits" encompassing, as a rule, a three-month period of follow-up. The study collected information on the general patient characteristics, medical care, and relevant outcomes. Patient enrolment was planned for 18 months. Patients were followed up for approximately 12 months during treatment with Sandostatin® LAR® before surgery and for up to about six months after surgery. The CRF included: baseline visit, four follow-up visits to collect data every three months before surgery, and two follow-up visits every three months after surgery. Sandostatin® LAR® was administered every four weeks. Because this was an observational study, it was assumed that in practice the frequency of follow-up visits could be different. Dates of visits were documented in CRFs. The duration of treatment of microadenomas was expected to be at least three months and up to six months, regarding macroadenomas it was at least six months and up to 12 months to obtain the maximum possible reduction of the concentrations of GH and IGF-1.

Efficacy assessments were performed by physicians according to standard practice, and if performed, they were reported in CRF. There were no study-related efficacy assessments. Efficacy parameters evaluated changes in GH and IGF-1 levels and tumour size reduction. Data from all sites were pooled and summarised with regard to demographic and baseline characteristics as well as to efficacy assessments. Stratification by type of adenoma allowed us to determine the final outcome specific to different adenomas. All primary variables were chosen before the start of the study. The efficacy measures assessed were as follows: changes of GH and IGF-1 levels, number of patients fulfilling criteria of cure as defined in the study protocol, and change of the size of adenomas (micro- and macroadenomas) during the treatment within the study.

Criteria of cure were the normalisation of IGF-1 (age- and sex-related) and GH concentration below 1.0 ng/mL. Assessment of changes in the adenoma size was performed for those patients for whom the data on three (70 pts.) or two dimensions (4 pts.) of the tumour, both during the initial visit and the preoperative visits, was available. Δ percentage change is defined as the relative reduction in adenoma size between the initial visit and the preoperative visit compared to the size at the initial visit, expressed as a percentage:

$$\Delta = (N1 - N2) / N1 * 100$$

where N1 is a measure of tumour size at initial visit, and N2 is a measure of the size of the tumour at preoperative visit.

If three dimensions were provided, a measure of the size of the tumour was expressed as tumour volume). If two dimensions were available, a measure of the size was expressed as the sum of the stated dimensions (measured circumference of the tumour).

Safety assessments consisted of monitoring and recording all adverse events (AE) and serious adverse events (SAE, with their severity and relationship to study drug) performed according to standard medical practice. AE and SAE were collected on every visit. SAE were reported according to the local procedures at the participating centre.

## *Statistical analysis*

Data from all collaborating sites were pooled and summarised with regard to demographic and baseline characteristics as well as to safety and efficacy assessment. Investigational analysis was performed using descriptive statistical methods. For quantitative variables the number of patients with feature variant (N) and its matching percentage were given (%), as well as basic descriptive characteristics: mean, median, max, min, quartiles (Q25 and Q75), and standard deviation (SD). Because the data were found not to be normally distributed, the non-parametric Mann-Whitney U test and the non-parametric Kruskall-Wallis analysis of variance were applied. For comparison of pre- and post-operation GH and IGF-1 concentrations the Wilcoxon test and the Friedman non-parametric analysis of variance were applied, together with the post-hoc Dunn test. For description of qualitative variable dependences, the chi-square test was used. To account for changes in numbers of patients with given pre- and post-operation GH and IGF-1 concentrations, McNemara and Bowker-McNemara tests were applied. Calculations were performed using LibreOffice package v. 3.4 (GPL — Open Source) and STATISTICA v. 7.1; a p-value $< 0.05$ was considered statistically significant.

## Results

The study also offered an insight into real-life acromegaly management in Poland at the time of the study. The proportion of female patients (59.5% initially and 62.5% finally) and their age were greater than those for the male patients (Tab. 1). The severity of most of the symptoms reported by patients was moderate (Tab. 2). Goitre, arterial hypertension, and glucose metabolism disturbances were the most common concomitant diseases among the patients studied (Tab. 3).

Eighty out of 148 patients completed the study (underwent pituitary adenoma surgery). The final results are given for this group.

The results of GH and IGF-1 concentrations at subsequent stages of the study are given in Table 4 and Figure 1 and 2. Initial GH concentration > 2.5 ng/mL was observed in 90.9% of patients, while in the remaining 9.1% it ranged from 1.0 to 2.5 ng/mL. There was no difference in these levels between males and females (p = 0.674). The patients with higher GH levels were 49.8 ± 11.4 years old, in comparison with patients with moderate GH elevation of 54.4 ± 4.9 years of age (p = 0.42). The estimated mean duration of the disease in patients with higher GH levels was 6.28 ± 5.28 years, against 4.67 ± 3.27 years (p = 0.591) for the remaining patients. Initial IGF-1 concentration > 1.3 upper limit of normal (ULN) was observed in 88.9% of patients; in the remaining 11.1% it varied in the range 1.0–1.3 ULN. Borderline higher IGF-1 values were observed in male patients (p = 0.075). The patients with higher IGF-1 values were 49.8 ± 11.8 years old, compared to patients with moderate IGF-1 increase of age 55.8 ± 6.0 years (p = 0.185). The estimated mean duration of the disease in patients with higher IGF-1 values was 6.1 ± 5.1 years, against 6.3 ± 1.7 years (p = 0.161) for patients with lower IGF-1 values. Seventy-five per cent of patients with microadenomas had GH levels > 2.5 ng/mL, against 96.4% of patients with macroadenomas (p = 0.008). 77.8% of patients with microadenomas had IGF-1 levels > 1.3 ULN, against 92.5% of patients with macroadenomas (p = 0.109).

**Table 4.** *Serum growth hormone (GH) and insulin-like growth factor 1 (IGF-1) concentrations in 80 patients with acromegaly at baseline, after somatostatin analogues SSA therapy, and after neurosurgery*

| Visit | GH [ng/mL] Mean ± SD | GH [ng/mL] Median | IGF-1 [ng/mL] Mean ± SD | IGF-1 [ng/mL] Median |
|---|---|---|---|---|
| Initial | 19.6 ± 21.0 | 12.8 | 789 ± 406 | 678 |
| Pre-surgical | 6.4 ± 9.4 | 2.9 | 477 ± 349 | 368 |
| Post-surgical | 2.3 ± 3.4 | 1.6 | 293 ± 304 | 192 |

SD — standard deviation

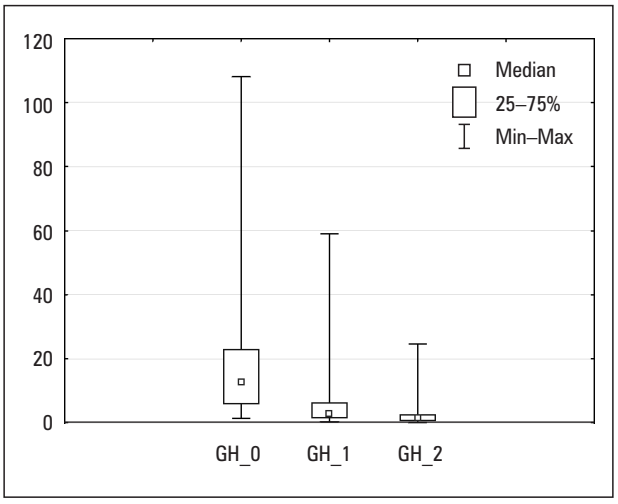


**Figure 1.** *Serum growth hormone (GH) concentrations in patients with acromegaly at baseline (GH_0), after somatostatin analogue (SSA) therapy (GH_1) and after neurosurgery (GH_2) ($\chi^2 = 98.09$, $df = 2$, $p < 0.00001$)*

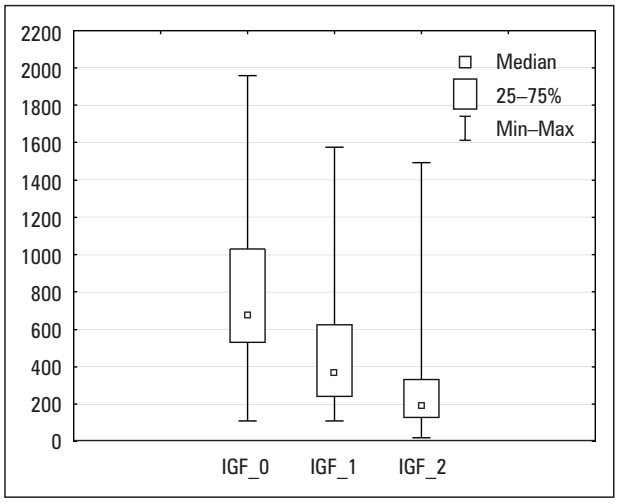


**Figure 2.** *Serum insulin-like growth factor 1 (IGF-1) concentrations in patients with acromegaly at baseline (IGF_0), after somatostatin analogues (SSA) therapy (IGF_1) and after neurosurgery (IGF_2) ($\chi^2 = 62.68$, $df = 2$, $p < 0.00001$)*

**Table 5.** *Proportion of serum growth hormone (GH) and insulin-like growth factor 1 (IGF-1) normalisation after somatostatin analogues (SSA) and neurosurgery in 80 patients with acromegaly*

| Visit | GH normal | GH > normal | IGF-1 normal | IGF-1 > normal |
|---|---|---|---|---|
| Pre-surgical | 42.4% | 57.6% | 49.1% | 50.9% |
| Post-surgical | 77.9% | 22.1% | 83.8% | 16.2% |

As the result of SSA therapy, reduction of microadenoma (n = 17) volume > 50% was obtained in one patient, 20–50% reduction in five patients, < 20% in four patients, and no reduction in the remaining seven. In patients with macroadenoma (n = 57) volume reduction > 50% was observed in 15 patients, 20–50% reduction in 13 patients, < 20% in 12, and no reduction in the remaining 17 patients.

During the SSA therapy the mean decrease of GH concentration was 44% of baseline value, 25% in patients with microadenomas, and 49% in patients with macroadenomas. Decrease of IGF-1 concentration was 37%, 26%, and 40%, respectively. Normalisation of GH and IGF-1 concentrations were obtained in 42.4 and 49.1% of patients at the end of their medical therapy, respectively (Tab. 5). Reduction of microadenoma size was documented in 58.8% of patients, and in 70.2% of patients with macroadenomas at the end of medical therapy.

Normalisation of GH and IGF-1 concentrations were obtained in 77.9 and 83.8% of patients after surgery, respectively (Table 5). In 74% of patients no signs of pituitary tumour were shown in post-operative MRI scans.

Treatment with Sandostatin® LAR® was well tolerated, which is shown by the small number of reported AEs. During the study transient loose stools were reported in two patients. This kind of AE was typical for the class of product and was consistent with information provided in Sandostatin® LAR® Summary of Product Characteristics (SPC). One SAE was qualified by the investigator as not related to study medication. The results of this non-interventional, observational post-marketing trial are in line with efficacy and safety data from SPC.

## Discussion

The study presented the therapeutic effect of pre-surgical treatment of patients with acromegaly with long-acting octreotide formulation, following the recommendations of the Polish Society of Endocrinology for the use of somatostatin analogues before surgery [5, 17].

Apart from results of pre-surgical SSA therapy, our study gave insight into real-life acromegaly management in Poland in the time of the study. Interestingly, in the group of 148 patients, the percentage and age of female patients was higher than those of male patients. Similar proportions occurred in other studies although, in general, acromegaly impacts both sexes equally [18]. The most numerous group according to age was sixth decade of life, in either sexes, the estimated duration of their disease being up to 10 years. The severity of symptoms reported by the patients was moderate, among them sweating was most oppressive and dyspnoea the least oppressive. The most common associated symptoms or complications of acromegaly in our patients were goitre, arterial hypertension, and glucose metabolism disturbances, which corroborates other studies [1, 3, 4, 19]. What was interesting in our group, diabetes mellitus, goitre, and heart failure were observed more often in female patients, and arterial hypertension in male patients. The majority of our patients had advanced disease, documented by the presence of macroadenoma in 75% of patients, baseline GH level > 2.5 ng/mL in 90.9%, and baseline IGF-1 level > 1.3 ULN in 88.9%. Higher IGF-1 values were observed in male patients. These data are concordant with other reports [3, 4].

Following SSA therapy greater reduction of adenoma size was observed in patients with macroadenomas than microadenomas, this observation confirming results of other studies [20, 21]. SSA therapy caused a decrease of GH and IGF-1 concentration by less than half of baseline values, leading to normalisation of GH and IGF-1 concentrations in 42.4 and 49.1% patients at the end of their medical therapy, respectively. Our results concur with results of other studies [3, 4]. Normalisation of GH and IGF-1 concentrations were obtained in 77.9 and 83.8% of patients after surgery, respectively. These values seem very promising and appear to be better than those reported elsewhere [3, 4].

The results of our study should be compared with conclusions of other reports, especially of meta-analyses reported quite recently. According to the first of these, pre-operative SSA increases the chance of biochemical control of acromegaly 3 months after transsphenoidal surgery in patients harbouring GH-secreting macroadenomas [13]. Another such meta-analysis reported on the safety of pre-operative SSA in acromegaly, and the favourable impact of

pre-operative SSA on surgical results was restricted to the short-term cure rate in macroadenomas and invasive macroadenomas [14]. In another study, pre-operative SSA significantly improved the results of surgery in centres without optimal surgical results; in such centres, patients with macroadenomas should be treated with a long-acting SSA prior to surgical treatment [15]. Pre-operative SSA treatment of GH-secreting pituitary tumours was beneficial in the group with short-term follow-up, while it was not advantageous in the group with long-term follow-up [16]. Well-designed randomised controlled trials to examine long-term results are awaited to clarify this dilemma [9, 14, 16].

Our results are similar to observations from other prospective studies. Six-months pre-operative octreotide might improve the surgical cure rate in newly diagnosed acromegalics with macroadenomas [9]. Pre-treatment with lanreotide before transsphenoidal surgery improved the surgical cure rates in patients with GH-secreting macroadenomas. Pre-treatment did not affect surgical complications or duration of hospital stay [22]. Pre-surgical long-acting octreotide treatment effectively reduced tumour size and invasion, which helps enhance early remission rates of invasive macroadenomas, but does not appear to improve the long-term cure rate [23].

Retrospective studies lead to similar conclusions. The long-term pre-operative SSA treatment may improve the surgical curative rate in acromegaly patients with invasive macroadenomas (Knosp grades 1-3) [24]. Pre-treatment with SSA could be recommended to patients with invasive macro- and giant adenomas for significant improvement in long-term remission [25]. Pre-surgical medical treatment significantly improved short- and long-term remission in patients with acromegaly, independently of its duration, especially in invasive adenomas [26]. There was a beneficial effect of pre-operative SSA use on early remission in macroadenomas; however, this effect did not persist in long-term observation [27].

Based on our results, pre-surgical SSA therapy, because it reduces the tumour size, could be beneficial for some patients with acromegaly, especially for those harbouring invasive macroadenomas, and in the surgery of high-risk subjects. Treatment with Sandostatin® LAR® was safe and well-tolerated. Typical AE were mild and transient.

Despite some limitations regarding the homogeneity of the group studied, different times of pre-surgical therapy, or lack of long-term post-surgical follow-up, the present study offers insight into real-life management of patients with acromegaly in Poland in a certain time. Another advantage of the study is the detailed clinical characteristics of a large group of Polish acromegalics.

In conclusion, we have shown good surgical outcome in patients with acromegaly after pre-treatment with long-acting somatostatin analogue, and good tolerance and safety of the medical therapy, supporting the national recommendation for pre-surgical treatment with somatostatin analogues in acromegaly.

### *Acknowledgements*

This study (CSMS995BPL03) was supported by Novartis Poland. The personal assistance of Dariusz Breński, Jan K. Żelazowski, Dorota Jurgilewicz, Sylwia Jaczewska, Grażyna Dzikielewska-Beranek, and Ewa Wąsak-Szulkowska is highly appreciated.

### *Other CSMS995BPL03 investigators*

Marcin Kałużny, Tomasz Tomkalski, Renata Tuchendler (Wrocław), Piotr Zdunowski, Krzysztof Chojnowski, Andrzej Jaroszuk (Warszawa), Paweł Bolko (Poznań), Marta Peszel-Barlik (Zabrze), Franciszek Mazur, Dorota Pakuła (Rybnik), Beata Matyjaszek-Matuszek, Maria Kurowska (Lublin), Teresa Gasińska (Katowice), Sonia Kaniuka, Krzysztof Błaut, Monika Berendt-Obołończyk, Renata Świątkowska-Stodulska, Barbara Wołyniak (Gdańsk), Joanna Tabora-Ciszewska, Elżbieta Łomna-Bogdanov, Agnieszka Florczak, Teresa Sicińska-Werner (Opole), Danuta Jakubczyk (Białystok), Krystyna Kowalczyk-Sobkowiak (Bielsko-Biała), Anna Piętka-Rzycka (Bytom), Urszula Słomian (Chorzów), Alicja Łuczyńska-Kołodziejczak (Gorzów Wielkopolski), Stanisław Kowarzyk (Nysa), Anna Wańczyk (Olsztyn).

## References

1. Melmed S. Medical progress: Acromegaly. N Engl J Med. 2006; 355(24): 2558–2573, doi: 10.1056/NEJMra062453, indexed in Pubmed: 17167139.
2. Bolfi F, Neves AF, Boguszewski CL, et al. Mortality in acromegaly decreased in the last decade: a systematic review and meta-analysis. Eur J Endocrinol. 2018; 179(1): 59–71, doi: 10.1530/EJE-18-0255, indexed in Pubmed: 29764907.
3. Katznelson L, Laws ER, Melmed S, et al. Endocrine Society. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014; 99(11): 3933–3951, doi: 10.1210/jc.2014-2700, indexed in Pubmed: 25356808.
4. Melmed S, Bronstein MD, Chanson P, et al. A Consensus Statement on acromegaly therapeutic outcomes. Nat Rev Endocrinol. 2018; 14(9): 552–561, doi: 10.1038/s41574-018-0058-5, indexed in Pubmed: 30050156.
5. Bolanowski M, Ruchała M, Zgliczyński W, et al. Diagnostics and treatment of acromegaly - updated recommendations of the Polish Society of Endocrinology. Endokrynol Pol. 2019; 70(1): 2–18, doi: 10.5603/EP.a2018.0093, indexed in Pubmed: 30843181.
6. Carmichael JD, Bonert VS, Nuño M, et al. Acromegaly clinical trial methodology impact on reported biochemical efficacy rates of somatostatin receptor ligand treatments: a meta-analysis. J Clin Endocrinol Metab. 2014; 99(5): 1825–1833, doi: 10.1210/jc.2013-3757, indexed in Pubmed: 24606084.
7. Colao A, Ferone D, Cappabianca P, et al. Effect of octreotide pretreatment on surgical outcome in acromegaly. J Clin Endocrinol Metab. 1997; 82(10): 3308–3314, doi: 10.1210/jcem.82.10.4283, indexed in Pubmed: 9329359.
8. Oshino S, Saitoh Y, Kasayama S, et al. Short-term preoperative octreotide treatment of GH-secreting pituitary adenoma: predictors of tumor shrinkage. Endocr J. 2006; 53(1): 125–132, doi: 10.1507/endocrj.53.125, indexed in Pubmed: 16543682.

9. Carlsen SM, Lund-Johansen M, Schreiner T, et al. Preoperative Octreotide Treatment of Acromegaly study group. Preoperative octreotide treatment in newly diagnosed acromegalic patients with macroadenomas increases cure short-term postoperative rates: a prospective, randomized trial. J Clin Endocrinol Metab. 2008; 93(8): 2984–2990, doi: 10.1210/jc.2008-0315, indexed in Pubmed: 18492760.
10. Biermasz NR, van Dulken H, Roelfsema F. Direct postoperative and follow-up results of transsphenoidal surgery in 19 acromegalic patients pretreated with octreotide compared to those in untreated matched controls. J Clin Endocrinol Metab. 1999; 84(10): 3551–3555, doi: 10.1210/jcem.84.10.6027, indexed in Pubmed: 10522994.
11. Plöckinger U, Quabbe HJ. Presurgical octreotide treatment in acromegaly: no improvement of final growth hormone (GH) concentration and pituitary function. A long-term case-control study. Acta Neurochir (Wien). 2005; 147(5): 485–93; discussion 493, doi: 10.1007/s00701-005-0511-9, indexed in Pubmed: 15806331.
12. Losa M, Mortini P, Urbaz L, et al. Presurgical treatment with somatostatin analogs in patients with acromegaly: effects on the remission and complication rates. J Neurosurg. 2006; 104(6): 899–906, doi: 10.3171/jns.2006.104.6.899, indexed in Pubmed: 16776333.
13. Nunes VS, Correa JMS, Puga MES, et al. Preoperative somatostatin analogues versus direct transsphenoidal surgery for newly-diagnosed acromegaly patients: a systematic review and meta-analysis using the GRADE system. Pituitary. 2015; 18(4): 500–508, doi: 10.1007/s11102-014-0602-9, indexed in Pubmed: 25261979.
14. Yang C, Li Ge, Jiang S, et al. Preoperative Somatostatin Analogues in Patients with Newly-diagnosed Acromegaly: A Systematic Review and Meta-analysis of Comparative Studies. Sci Rep. 2019; 9(1): 14070, doi: 10.1038/s41598-019-50639-6, indexed in Pubmed: 31575930.
15. Pita-Gutierrez F, Pertega-Diaz S, Pita-Fernandez S, et al. Place of preoperative treatment of acromegaly with somatostatin analog on surgical outcome: a systematic review and meta-analysis. PLoS One. 2013; 8(4): e61523, doi: 10.1371/journal.pone.0061523, indexed in Pubmed: 23634209.
16. Zhang L, Wu X, Yan Y, et al. Preoperative somatostatin analogs treatment in acromegalic patients with macroadenomas. A meta-analysis. Brain Dev. 2015; 37(2): 181–190, doi: 10.1016/j.braindev.2014.04.009, indexed in Pubmed: 24815226.
17. Bolanowski M, Bar-Andziak E, Kos-Kudła B, et al. [Konsensus Polskiego Towarzystwa Endokrynologicznego. Przygotowanie analogami somatostatyny do leczenia operacyjnego akromegalii]. Endokrynol Pol. 2007; 58(4): 350–353, indexed in Pubmed: 18058727.
18. Petrossians P, Daly AF, Natchev E, et al. Acromegaly at diagnosis in 3173 patients from the Liège Acromegaly Survey (LAS) Database. Endocr Relat Cancer. 2017; 24(10): 505–518, doi: 10.1530/ERC-17-0253, indexed in Pubmed: 28733467.
19. Melmed S, Casanueva FF, Klibanski A, et al. Pituitary Society and the European Neuroendocrine Association. Diagnosis and treatment of acromegaly complications. J Endocrinol Invest. 2003; 26(12): 1242–1247, doi: 10.1007/BF03349164, indexed in Pubmed: 15055479.
20. 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(4): 1397–1403, doi: 10.1210/jc.2005-2347, indexed in Pubmed: 16449332.
21. Caron PJ, Bevan JS, Petersenn S, et al. PRIMARYS Investigators. Tumor shrinkage with lanreotide Autogel 120 mg as primary therapy in acromegaly: results of a prospective multicenter clinical trial. J Clin Endocrinol Metab. 2014; 99(4): 1282–1290, doi: 10.1210/jc.2013-3318, indexed in Pubmed: 24423301.
22. Mao Zg, Zhu Yh, Tang Hl, et al. Preoperative lanreotide treatment in acromegalic patients with macroadenomas increases short-term postoperative cure rates: a prospective, randomised trial. Eur J Endocrinol. 2010; 162(4): 661–666, doi: 10.1530/EJE-09-0908, indexed in Pubmed: 20061334.
23. Shen M, Shou X, Wang Y, et al. Effect of presurgical long-acting octreotide treatment in acromegaly patients with invasive pituitary macroadenomas: a prospective randomized study. Endocr J. 2010; 57(12): 1035–1044, doi: 10.1507/endocrj.k10e-203, indexed in Pubmed: 21099129.
24. Duan L, Zhu H, Xing B, et al. Prolonged preoperative treatment of acromegaly with Somatostatin analogs may improve surgical outcome in patients with invasive pituitary macroadenoma (Knosp grades 1-3): a retrospective cohort study conducted at a single center. BMC Endocr Disord. 2017; 17(1): 55, doi: 10.1186/s12902-017-0205-3, indexed in Pubmed: 28874187.
25. Lv L, Hu Yu, Zhou P, et al. Presurgical treatment with somatostatin analogues in growth hormone-secreting pituitary adenomas: A long-term single-center experience. Clin Neurol Neurosurg. 2018; 167: 24–30, doi: 10.1016/j.clineuro.2018.02.006, indexed in Pubmed: 29433055.
26. Albarel F, Castinetti F, Morange I, et al. Pre-surgical medical treatment, a major prognostic factor for long-term remission in acromegaly. Pituitary. 2018; 21(6): 615–623, doi: 10.1007/s11102-018-0916-0, indexed in Pubmed: 30367444.
27. Polat Korkmaz O, Gurcan M, Nuhoglu Kantarci FE, et al. The effects of pre-operative somatostatin analogue therapy on treatment cost and remission in acromegaly. Pituitary. 2019; 22(4): 387–396, doi: 10.1007/s11102-019-00968-6, indexed in Pubmed: 31098838.