Effectiveness of somatostatin analogs as first-line or second-line treatment in acromegaly: single centre experience

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Introduction:

Acromegaly is a chronic disorder characterised by hypersecretion of growth hormone (GH), which leads to the increased production of IGF-I (1). In the majority of patients (>95%) it results from a GH-secreting pituitary adenoma (1). With the incidence of 3 to 4 new cases per million and the prevalence of 40 to 125 per million, acromegaly is a rare disease (2). Acromegaly affects almost every organ and is associated with increased morbidity and mortality and reduced quality of life. Increased mortality is reverted to that of the normal population after normalization of GH and IGF-I levels by successful treatment (3). Transsphenoidal surgery remains the cornerstone of management for most patients with acromegaly, resulting in disease control in >85% of patients with microadenomas and in 40-50% of those with macroadenomas (4). Because complete resection is not always feasible, adjunctive therapy is frequently necessary. Somatostatin analogs (SSA) are the most widely used medications to control GH hypersecretion after failure of surgery or as primary medical therapy in selected patients (5). IGF-1 normalization achieved by SSA treatment in unselected patients is 17-35% (4, 5) and remains disputable. The purpose of this study was to evaluate and compare disease outcomes in patients with acromegaly receiving first-line and second-line (after transsphenoidal surgery) SSA treatment.

Patients and methods:

It was a retrospective study conducted in the centre of Endocrinology in Vilnius University hospital Santariškių klinikos, a tertiary referral centre for endocrinology and diabetes mellitus. Data of 49 patients who were diagnosed, treated or followed-up because of acromegaly between 2007 and 2013 were extracted from the hospital's electronic database. In all cases diagnosis of acromegaly was established on the basis of characteristic clinical features, elevated for age and gender IGF-I, and failure to suppress GH < 3 mIU/l after 75 g oral glucose tolerance test (OGTT) or elevated random GH level. Magnetic resonance imaging (MRI) was performed in all patients except one in whom computerized tomography was done because of contraindications to MRI. Tumor size was classified as micro- (<10 mm) and macroadenoma. The following data were collected from medical records: demographic features, date of diagnosis, tumor size, hormonal data (initial and follow-up IGF-I and GH levels). Details on treatment (number and method of surgical treatment, previous and current medical therapy and whether it was primary therapy, radiotherapy date and method) were also registered.

Disease remission was defined according to the latest guidelines (4): normal age- and gender-adjusted IGF-I, and nadir GH < 3 mIU/l after 75 g OGTT or random GH < 3 mIU/l. Partial disease control was documented according local acromegaly management guidelines in cases when IGF-I level dropped, but remained <30% above upper limit of normal (adjusted for age and gender), and random GH was below 7.5 mIU/l. Uncontrolled disease was defined in cases when IGF-I level was elevated >30% above age- and gender-adjusted upper limit of normal and random GH was above 7.5 mIU/l. In case of discordant IGF-I and GH results, a patient was assigned to one of study groups according to worse result. Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) 15.0 software.

Table 1. Characteristics of study population

Patient population	N (%)
Male	16/49 (32.7%)
Female	33/49 (67.3%)
Age at diagnosis (yr) (mean ± SD)	54.5±13
Tumor characteristics	
Microadenoma	14/42 (33.3%)
Macroadenoma	28/42 (66.7%)

Table 2. Treatment modalities and disease outcomes

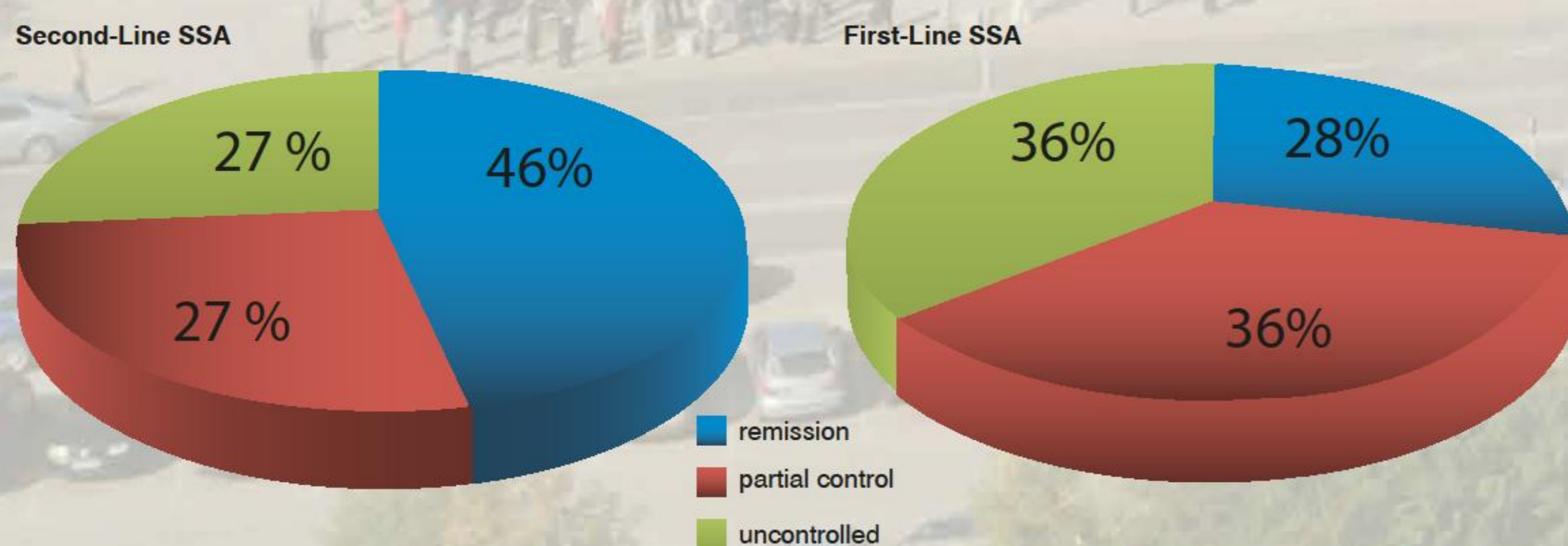|		
Transsphenoidal surgery		31/47 (66.0 %)
	Remission	10/31 (32.3%)
	Partial control	5/31 (16.1%)
	Uncontrolled	16/31 (51.6%)
Second-line SSA treatment		15/47 (35.7%)
	Remission	7/15 (46.7%)
	Partialcontrol	4/15 (26.7%)
	Uncontrolled	4/15 (26.7%)
First-line SSA therapy		14/47 (29.8%)
	Remission	4/14 (28.6%)
	Partial control	5/14 (35.7%)
	Uncontrolled	5/14 (35.7%)
Primary radiotherapy	Remission	1/47 (2.1%)

Results

Demographics and clinical data

49 patients (26 newly diagnosed and 23 followed-up or treated) were included in the analysis. Patient population consisted of 16 males and 33 females with a mean age at diagnosis of 54.5±13 years. All cases except two (empty sella) were caused by pituitary adenomas, of which 66.7% were macroadenomas and 33.3% were microadenomas (table 1). Data about pituitary adenoma preoperative size were not found in the charts in five cases.

Results of treatment

Transsphenoidal operation was applied as the first-line therapy in 31 patients and it led to disease remission in 10 of them (partial disease control was achieved in 5 of operated patients). Primary SSA therapy was administered in 14 of cases due to contraindications or refusal of surgery. One patient was not administered any treatment because of severe comorbidities, one was treated with primary radiotherapy. In two cases data about treatment is not available as the patients are lost to follow-up. Of surgically treated patients, 15 received second-line SSA therapy because of uncontrolled disease. Radiotherapy as a third-line treatment was applied in the 5 (33%) patients with a postoperative disease recurrence (table 2). Based on the latest GH and IGF-1 results, control and partial control were achieved in 4 (28.6%) and 5 (35.7%) patients in first-line SSA therapy group, and in 7 (46.7%) and 4 (26.7%) patients in second-line SSA therapy group. 5 (35.7%) and 4 (26.7%) of patients in first-line and second-line SSA treatment groups remained uncontrolled (figure 1).

Figure 1. Disease outcomes in second-line SSA and first-line SSA treatment groups

Second-Line SSA — remission 46%, partial control 27%, uncontrolled 27%
First-Line SSA — remission 28%, partial control 36%, uncontrolled 36%

- remission
- partial control
- uncontrolled

Based on the latest GH and IGF-1 results, in the whole study population the outcomes were: 46.8% cured or controlled, 29.8% partially controlled, and 23.4% uncontrolled (Figure 2).

Figure 2. Disease outcomes in study population

Study population

- 22 (47%) remission
- 14 (30%) partial control
- 11 (23%) uncontrolled
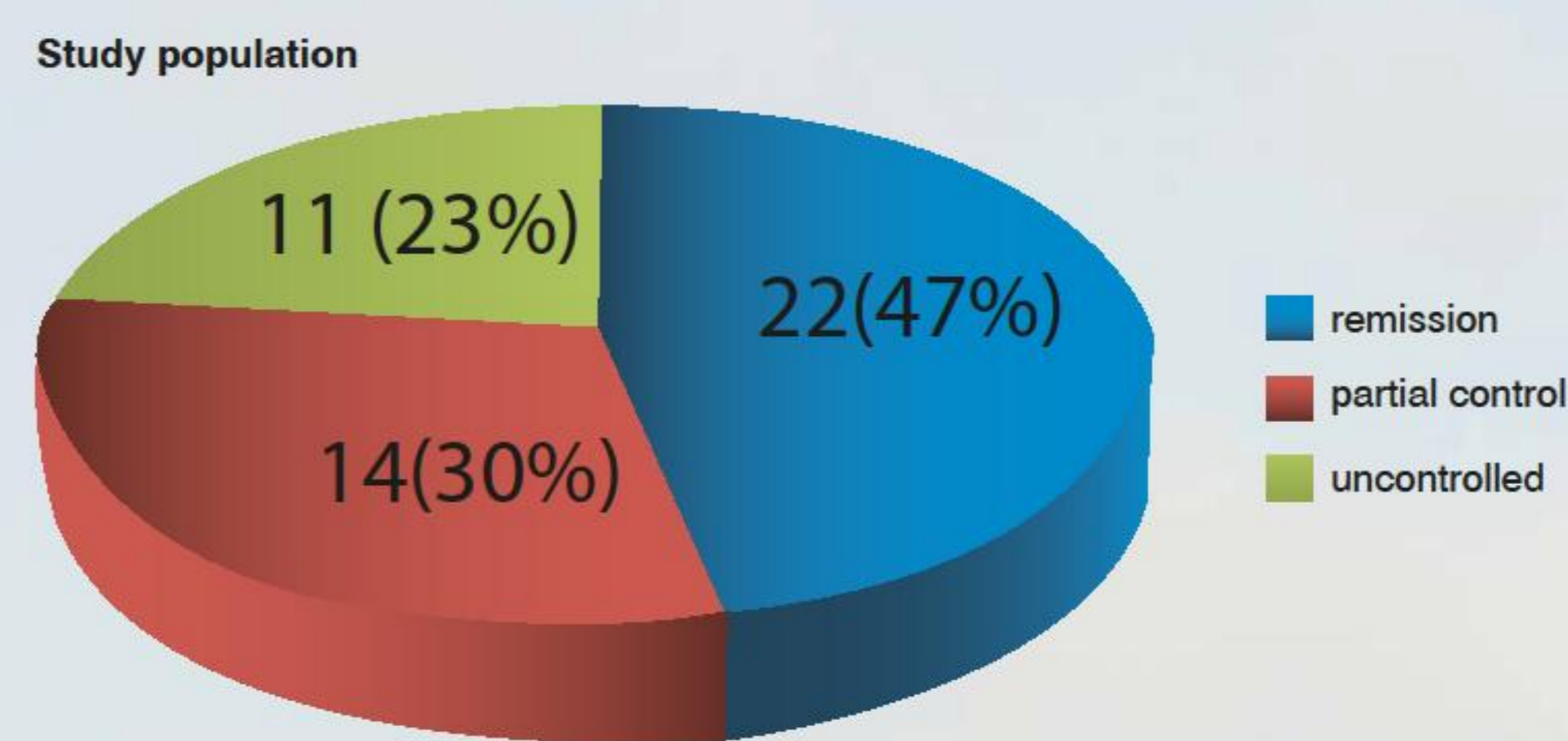
IGF-1 and GH levels in medically treated patients

Although we observed higher mean observational period IGF-1 in the first-line SSA treatment group (511.0 [230.9; 791.1] µg/l) as compared to second-line SSA therapy group (403.3 [280.3; 526.2] µg/l), the difference did not reach statistical significance (p=0.384) (figure 3).

Figure 3. Observational period mean IGF-1 in second-line and first-line SSA treatment groups combination treatment groups, p=0.384
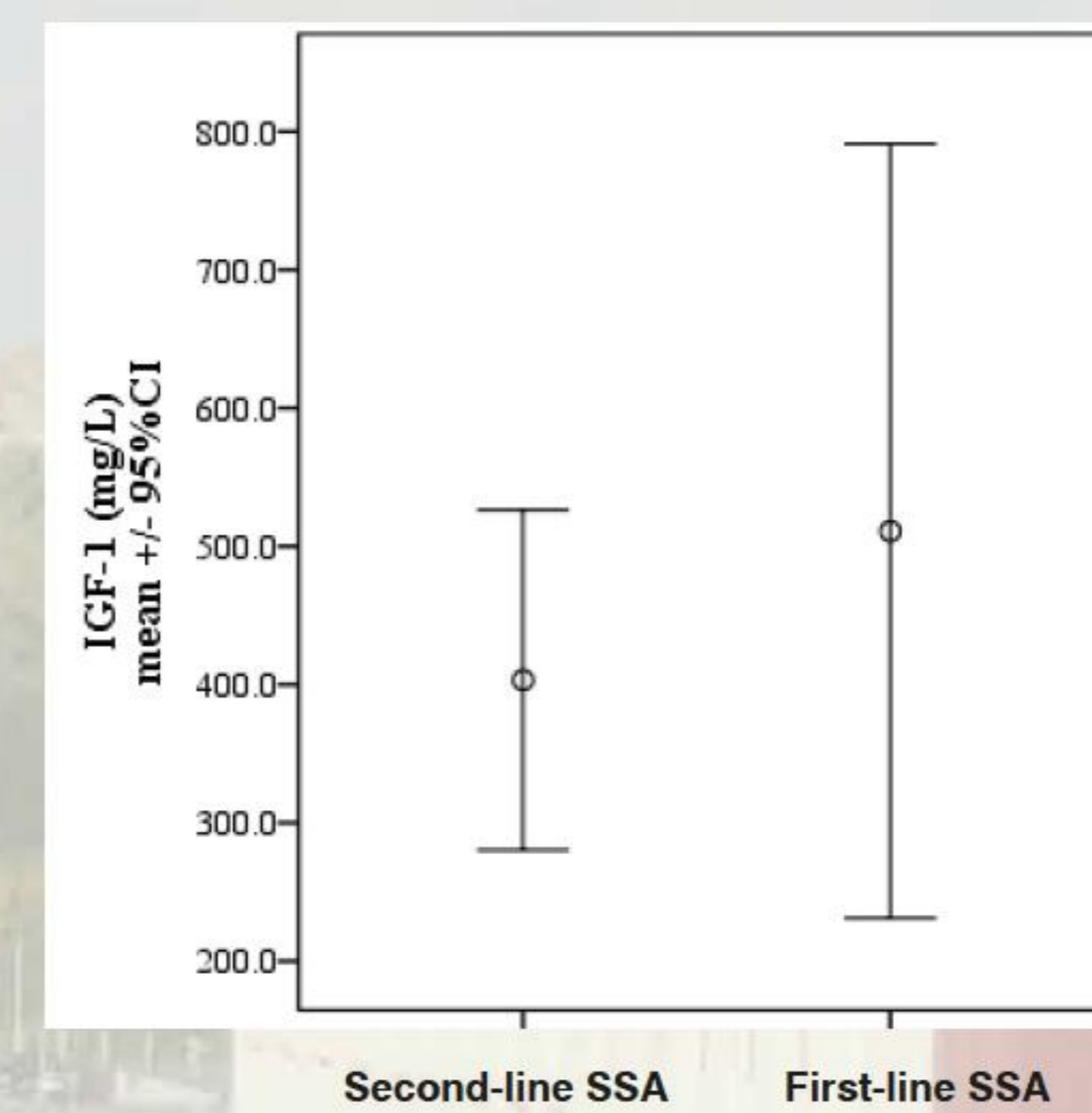
Mean GH in these groups were also not statistically significantly different: 7.1 [2.7; 11.6] mIU/l vs. 8.5 [3.2; 13.9] mIU/l, p=0.647) (figure 4).

Figure 4. Observational period mean GH in second-line SSA and first-line SSA treatment groups (P=0.647)
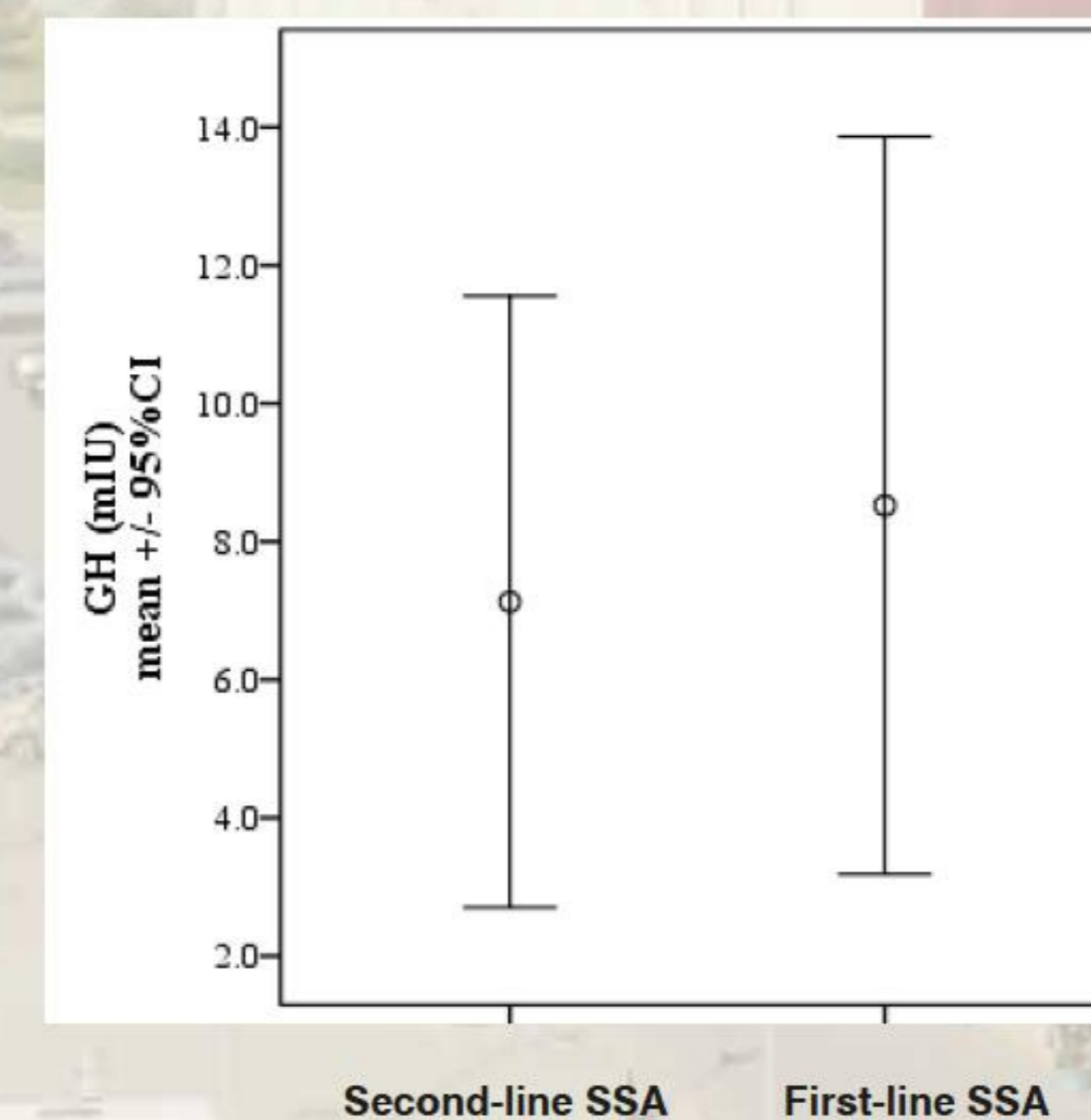
Conclusions:

SSAs are more effective in the treatment of acromegaly when applied after transsphenoidal surgery, as they help to achieve control of the disease in a greater percentage of patients. We observed higher observational period IGF-1 and GH levels in first-line SSA treatment patients when compared to second-line SSA treatment patients, although the differences did not reach statistical significance. Control of the disease remains a challenge despite availability of high-dose SSA treatment as 27-36% of patients receiving primary or second-line SSA treatment remain uncontrolled.

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