The efficacy of medical treatment in patients with acromegaly in clinical practice

Seo Young Lee¹, Jung Hee Kim², Ji Hyun Lee¹, Yong Hwy Kim³, Hyang Jin Cha¹, Sang Wan Kim¹,⁴, Sun Ha Paek¹,² and Chan Soo Shin¹,²

¹) Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea
²) Pituitary Center, Seoul National University College of Medicine, Seoul, Republic of Korea
³) Department of Neurosurgery, Seoul National University College of Medicine, Seoul, Republic of Korea
⁴) Department of Internal Medicine, Seoul Metropolitan Government Boramae Medical Center, Seoul, Republic of Korea

Abstract. Although somatostatin analogues (SSAs) are recommended as the first-line medical therapy for acromegaly, dopamine agonists (DAs) are also a therapeutic option for treatment. We aimed to assess and compare the efficacies of DAs and SSAs in treating acromegaly in clinical practice. We included 89 patients with acromegaly who took DAs (bromocriptine [BCT], n = 63; cabergoline [CAB], n = 11) or SSAs (n = 15) as a primary medical therapy for more than 3 months in the Seoul National University Hospital. The CAB (45.5%) and SSA (33.3%) groups achieved random GH levels of <2.5 ng/mL and the normal IGF-1 levels were significantly higher than in the BCT group (11.1%) (p = 0.009). We further included all the patients with acromegaly (n = 132) who had taken CAB, BCT, and SSAs as first- or second-line medical therapy. The CAB group showed similar efficacy as the SSA group in terms of the GH and insulin-like growth factor-1 (IGF-1) levels (57.6% for random GH level <2.5 ng/mL, 42.4% for normal IGF-1 levels, 36.4% for both). Logistic regression analysis revealed that medications, age, GH level, or IGF-1 level before medication, hyperprolactinemia, and prior gamma-knife surgery or radiation therapy, did not affect the therapeutic response. High pretreatment GH levels predicted poor treatment outcomes (odds ratio [95% confidence interval] = 0.95 [0.90–0.99]). CAB was effective in treating acromegaly at a relatively lower cost in patients with low pretreatment GH levels.

Key words: Acromegaly, Dopamine agonists, Somatostatin analogues, Cabergoline, Bromocriptine

ACROMEGALY is a rare disease complicated by cardiovascular, cerebrovascular, and respiratory diseases, leading to the high mortality [1]. Therefore, the control of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels in patients with acromegaly is an important issue to prevent comorbidities [2]. According to previous studies, there was no significant difference in the mortality between patients with acromegaly and healthy subjects, when maintaining a random GH level below 2.5 ng/mL [3] and IGF-1 level below the upper limit of normal (ULN) [4].

Surgical resection is usually considered as a first-line therapy for acromegaly, but the success rate varies from >85% for microadenomas to 40–50% for macroadenomas even with experienced pituitary surgeons performing the operation [5-9]. A considerable number of patients harbor invasive pituitary adenomas, which are not surgically curable. Moreover, the 5-year disease recurrence rates ranged from 2–8% [5]. Therefore, when surgery fails to control the tumor control, medical therapy can be considered as a second-line treatment.

The currently available medications include somatostatin analogs (SSAs), dopamine agonist (DAs), and GH receptor antagonists. Since the GH receptor antagonist (pegvisomant) was not available in Korea, there were only two options, SSAs and DAs such as bromocriptine (BCT) or cabergoline (CAB). DAs have been known to suppress prolactin secretion i.e. in prolactinomas, but they have an additional effect in acromegaly. It was observed that DAs suppressed the D2 receptor in GH-producing pituitary adenomas, which can inhibit GH secretion successfully in patients with acromegaly [10].
However, whether or not CAB treatment is useful in acromegaly remains controversial [11].

Considering their mechanism of action, SSAs have been recommended as a primary medical therapy, as several studies have reported IGF-1 normalization rates of up to 63% and tumor shrinkage rates up to 70% [12-14]. However, in unbiased patients, the treatment response rate of SSAs was also reportedly lower than expected, with a mean efficacy rate of 31% [15]. The high cost and injection form limited the use of SSAs in Korea. Due to the convenience and low cost of oral administration, DAs have been widely used in Korea.

We aimed to investigate and compare the efficacies of DA, i.e., CAB, and SSAs in treating acromegaly in clinical practice, and also identify the predictors of treatment response.

**Materials and Methods**

**Study participants**

We included 130 patients with acromegaly in this retrospective cohort. The patients were not biochemically controlled and experienced medical treatment after surgery or radiation therapy from Seoul National University Hospital from Jan 2000 to May 2016. The patients were diagnosed with active acromegaly if they had elevated serum GH levels not suppressed below 1 ng/mL after a 75-g oral glucose load and elevated serum IGF-1 levels above the normal range for their age. All data were retrieved from the medical records retrospectively. The data included the patients’ age at diagnosis, history of surgery with pathology, radiation therapy or gamma-knife surgery GKS, medication history for acromegaly with dose information, hormone profiles (including GH, IGF-1, prolactin levels), and tumor size from magnetic resonance imaging (MRI). Among the 130 patients who underwent medical treatment, 41 patients who were on the medication for less than 3 months and began medical treatment before 2000 were excluded. In the final analysis, a total of 89 patients were included. The study was approved by the Institutional Review Board of the Seoul National University Hospital (IRB no. 1503-040-654).

Dopamine agonists (DAs) and somatostatin analogues (SSAs) were provided as an adjunctive treatment to patients who were not cured after surgical or radiation therapy or who refused to undergo the operation. Medical therapy was not considered as a primary treatment. We classified the first and second-line medical treatment, and the analyses were done separately by only first-line medical treatment ($n = 89$) and first plus second-line medical treatment ($n = 132$) (Fig. 1). DAs included CAB and BCT, while SSAs included octreotide and lanreotide. Eleven CAB users continue their medications, and among the 63 BCT users, 17 and 19 patients changed their medication into CAB and SSA, respectively. Out of the 15 SSA users, CAB and BCT were used in 5 and 2 patients, respectively. Finally, there were 33 CAB, 65 BCT, and 34 SSA users in our study sample.

Among the total 89 patients administered first-line medication, medication was changed for 43 patients from first-line to second-line medication. Since medication was not changed for any patient from CAB to the second-line drug, 36 patients receiving first-line BCT and 7 patients receiving first-line SSA, whose medication was changed to the second-line drug, were reviewed. BCT was discontinued for 23 (63.9%) patients and SSA was discontinued for 7 (100.0%), owing to the lack of efficacy. BCT was discontinued for 6 users (16.7%)
owing to gastrointestinal side effects. Furthermore, 3 (8.3%) patients were lost to follow-up. In 4 patients, the reason for switching medication was inconvenience. Hence, drugs were changed from first-line to second-line medication.

The outcomes to evaluate the efficacy of the medications were defined as follows: a response was defined as positive when the random GH level was under 2.5 ng/mL and/or the IGF-1 level was under the upper limit of ULN [11, 16, 17].

**Hormone measurement**

The GH levels were measured by an immunoradiometric assay kit (Izotope, Budapest, Hungary) with intra-assay coefficients of variation (CV) of 1.5–3.5% and inter-assay CVs of 2.5–3.3%. The IGF-1 levels were estimated using an immunoradiometric assay kit (Beckman Coulter, California, USA) with intra-assay CVs of less than 5.6% and inter-assay CVs of less than 8.3%. The lowest detectable levels of GH and IGF-1 were 0.02 and 4.55 ng/mL, respectively. The World Health Organization international standards for GH (88/624) and IGF-1 (87/518) measurement were used. The IGF-1 levels were presented as multiples of the ULN. The definition of GH and IGF-1 values after medical treatment was the last observed values during the follow-up evaluation. The serum prolactin was measured using a conventional immunoradiometric assay (Shinjin Medics Inc., Goyang Si, Korea).

**Statistical analysis**

The qualitative variables are presented as n (%) and the continuous variables as medians with interquartile ranges (IQR). The chi-square test or Mann-Whitney U test was used to compare the categorical and continuous variables. The Kruskal-Wallis test was used to compare continuous variables among the three groups. Logistic regression models were used to evaluate the predictive factors for responses to medical therapy including the type of medication, age at diagnosis, GH level before medication, IGF-1 level before medication, hyperprolactinemia, prior therapy of GKS or radiation, and treatment duration. All statistical analyses were performed using the SPSS software (version 22; SPSS Inc., Chicago, IL), and differences with a p-value of less than 0.05 were considered statistically significant.

**Results**

The baseline characteristics of the CAB (n = 11), BCT (n = 63), and SSA (n = 15) groups are shown in Table 1. The median doses of medications were 2.0 (IQR, 1.0–3.0) mg/week for CAB and 15.0 (IQR, 10.0–22.5) mg/day for BCT. In the SSA group, 9 patients took octreotide LAR and 4 patients took lanreotide autogel. The patients using SSAs (35 years) were significantly younger (p = 0.002) than patients using CAB (43.5 years) or BCT (41.5 years). There were no differences in the sex or BMI among the groups. The initial serum GH, IGF-1 levels, tumor size, invasiveness, and prior therapy were not significantly different among the three groups.

Before medical treatment, the serum GH level was higher in the SSA group (15.1 [9.0–34.8] ng/mL) than the CAB (5.10 [3.48–7.23] ng/mL) or BCT (7.38 [4.65–16.7] ng/mL) groups (p = 0.010), while the serum IGF-1 level and tumor size were not statistically different between the groups. We compared the therapeutic responses to CAB, BCT, and SSA in patients with first-line medical therapy (Table 2). After the medical therapy, the CAB (median, 1.71 ng/mL) and SSA (median, 1.70 ng/mL) groups had lower GH levels than the BCT group (median, 3.49 ng/mL); on the other hand, the IGF-1 levels after medical therapy were similar in all the groups. However, the percentage of GH reduction was more prominent in the SSA group (median, –85.4%) than in the CAB group (median, –54.7%) since the GH levels before treatment were higher in the SSA group than in the CAB group. The proportion of patients with a random GH level <2.5 ng/mL was significant lower in the BCT group (23.8%) compared to that in the CAB group (63.6%) and the SSA group (46.7%). There was no significant difference in IGF-1 normalization and random GH level <2.5 ng/mL or normal IGF-1 among the three groups. The CAB (45.5%) and SSA (33.3%) groups had significantly higher random GH levels <2.5 ng/mL and normal IGF-1 levels than the BCT group (11.1%) (p = 0.009). The treatment duration was similar among all the groups.

We further included all the patients (n = 132) acromegaly who had taken CAB, BCT, and SSAs as first- or second-line medical therapy (Table 3). The degree of GH reduction was larger in the SSA group than in the CAB or BCT groups, although the GH level after medical therapy was lowest in the CAB group. The IGF-1 level after medical therapy was lowest in the SSA group. More patients in the CAB group achieved random GH levels
<2.5 ng/mL (57.6% vs. 23.1%, \( p = 0.001 \)) and random GH levels <2.5 ng/mL with IGF-1 normalization (36.4% vs. 10.8%, \( p = 0.004 \)) than those in the BCT group. The SSA group had similar efficacy as the CAB group in terms of the GH and IGF-1 levels (38.2% for GH <2.5 ng/mL, 50.0% for normal IGF-1 levels, 26.5% for both).

For the tumor shrinkage, we analyzed only the evaluable cases of tumor shrinkage which was 15, 30 and 14 cases for CAB, BCT and SSA. The mean tumor shrinkage percent was 24.2 (0.0–47.9) %, 17.7 (0.0–45.0) % and 0.0 (–18.3–99.9) % for CAB, BCT and SSA but the difference were not statistically significant.

Furthermore, we compared the therapeutic response of the same patients for whom medication was switched (Supplementary Table 3). Given that GH and IGF-I levels before medical treatment were similar during BCT and CAB treatment, CAB was more effective in lowering GH and IGF-I levels than was BCT. SSA lowered GH and IGF-I levels after treatment even further than did BCT, but the pretreatment IGF-I level was lower in the SSA than in the BCT group. Therefore, we further adjusted the pretreatment IGF-I (percentage of ULN) level, but there was no significant difference between two groups.

We performed the logistic regression analysis for controlled disease (both random GH level <2.5 ng/mL and normal IGF-1) for medications in patients with acromegaly (Table 4 and Supplementary Table 1). In all the patients regardless of first-line or second-line medical therapy, CAB and SSA treatment provided better responses compared to BCT treatment, and CAB exhibited similar efficacy as SSA. CAB and SSA displayed greater efficacy than did BCT even after adjusting for pretreatment GH levels. However, the therapeutic efficacy of CAB and SSA were not significantly different after adjusting for pretreatment GH levels. However, age, IGF-1 level before medication, hyperprolactinemia, prior therapy of GKS or radiation, and treatment duration did not affect the therapeutic response. Only high pretreatment GH levels predicted poor clinical outcomes (odds ratio [95% confidence interval] = 0.95 [0.90–0.99]).

During treatment with first-line and second-line medication, 24 patients complained of the following side
Discussion

The present study showed that the efficacy of CAB was not inferior to that of SSAs, but superior to that of BCT, using random GH level <2.5 ng/mL and normal IGF-1 as the criteria. SSAs were prescribed in younger patients with higher GH levels compared to CAB or BCT. While SSA reduced the GH levels more dramatically, the GH levels after medical therapy were not different between the SSA and CAB groups, since the pretreatment GH levels were higher in the SSA group than in the CAB group. Even after adjusting for the GH levels before medication, CAB was comparable to SSA in treating acromegaly. High GH levels before treatment predicted the poor response to medical treatment.

Previous studies have questioned the efficacy of CAB in treating acromegaly due to the lack of randomized controlled trials and small sample sizes of the existing trials [18-24]. Abs et al. reported the effect of long-term administration of CAB in a relatively large group, indicating that the IGF-1 levels were below 300 μg/L in 39% and the GH levels below 2 μg/L in 46% of the patients [19]. While the results were similar to our data (IGF-1...
normalization, 45.5%), age-specific IGF-1 normalization was not presented in the study by Abs et al.; these results cannot be compared with those from other studies. Recently, a meta-analysis showed that IGF-1 normalization was achieved in 34% of the CAB-treated patients [11]. However, the study was criticized as it included only 160 patients from 10 retrospective studies and cases with short treatment durations [11]. Moreover, the UK acromegaly registry published that GH and IGF-1 both normalized in 55% of the patients on SSA (n = 923) and 36% of the patients on CAB (n = 353) [25]. The treatment outcome of CAB was lower than observed in our study (45.5%), which can be attributed to the different criteria of GH control and different assay kits used. In addition, the patients treated with CAB in our study may have a less severe disease than the patients in other studies.

Accordingly, the recent Endocrine Society Guideline placed CAB in the third place after SSA and pegvisomant [5]. Nevertheless, since pegvisomant was not introduced in Korea and SSA was expensive and injectable, DAs have been widely used in actual practice. Given that CAB was introduced only recently and not allowed for use in acromegaly treatment, BCT was widely used in our hospital. We confirmed the low efficacy of BCT compared to that of CAB and SSA, which had already been reported by others [26]. Due to the wide use of BCT in our study subjects, the number of patients treated by CAB or SSA was small and the statistical power of our results was weak. Hence, we collected all data that recorded BCT, CAB, or SSA as first- or second-line medical treatment. The above method increased the effective sample size. The percentage of patients with

<table>
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<th>Table 3</th>
<th>Comparison of therapeutic responses to cabergoline (CAB), bromocriptine (BCT), and somatostatin analogs (SSAs) in patients with first or second-line medical therapy (n = 132)</th>
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<tbody>
<tr>
<td>Age at diagnosis</td>
<td>CAB (n = 33)</td>
</tr>
<tr>
<td>Before first or second medical treatment</td>
<td>46 (37–56)</td>
</tr>
<tr>
<td>GH before treatment (ng/mL)</td>
<td>3.72 (2.15–8.13)</td>
</tr>
<tr>
<td>IGF-I before treatment (% of ULN)</td>
<td>173 (119–224)</td>
</tr>
<tr>
<td>Duration of treatment (months)</td>
<td>26.5 (16.0–39.0)</td>
</tr>
<tr>
<td>After medical treatment</td>
<td></td>
</tr>
<tr>
<td>GH (ng/mL)</td>
<td>1.69 (0.80–4.50)</td>
</tr>
<tr>
<td>% Change in GH</td>
<td>–54.9 (–77.2–~7.0)</td>
</tr>
<tr>
<td>IGF-I (% of ULN)</td>
<td>113 (82–177)</td>
</tr>
<tr>
<td>% Change in IGF-I</td>
<td>–25.4 (~39.7–~2.2)</td>
</tr>
<tr>
<td>GH &lt;2.5 ng/mL (%)</td>
<td>19 (57.6%)</td>
</tr>
<tr>
<td>Normal IGF-I (%)</td>
<td>14 (42.4%)</td>
</tr>
<tr>
<td>GH &lt;2.5 ng/mL and normal IGF-I (%)</td>
<td>12 (36.4%)</td>
</tr>
<tr>
<td>Number of evaluable cases of tumor shrinkage</td>
<td>15</td>
</tr>
<tr>
<td>Tumor shrinkage percent</td>
<td>24.2 (0.0–47.9)</td>
</tr>
<tr>
<td>Median dose</td>
<td>4.0 mg/week (2.0–18.8)</td>
</tr>
<tr>
<td>Lane 60.0 mg/4 weeks (28.8–83.2)</td>
<td></td>
</tr>
<tr>
<td>Side effects (%)</td>
<td>7 (23.3%)</td>
</tr>
<tr>
<td>Previous last radiation time to last medication time (months)</td>
<td>97.5 (82.5–140.8)</td>
</tr>
</tbody>
</table>

Values are median (interquartile range) or n (%). ULN, upper limit of normal. a, p < 0.05 between CAB and BCT; b, p < 0.05 between CAB and SSA; c, p < 0.05 between BCT and SSA. The values for GH and IGF-1 levels before second-line treatment were just before the beginning of second-line medication and after the first-line treatment.
random GH level <2.5 ng/mL and normal IGF-1 was reduced by about 10% compared to that seen in the analysis of only first-line users. The efficacy of CAB was 36.4%, which was much similar to that reported by previous studies [11, 19].

The efficacy of SSAs has been reported to range from 51% to 63% for GH or IGF-1 normalization [27, 28]. However, the composite efficacy for both GH and IGF-1 normalization (range, 20–54%) was less than the individual efficacy for GH or IGF-1 normalization [15, 29]. The biochemical response rates with SSAs depend on the context of the study such as the inclusion criteria, composite endpoints, treatment durations, and first or second-line therapy. Moreover, the discordance between GH and IGF-1 level was observed in 5.4–40% of the patients with acromegaly [30] due to differences in the sensitivities of the assays used [31]. Despite considering this, the treatment efficacy of SSAs in the present study (26.5–33.3%) was much lower than that reported by previous studies. First, the different criteria for endpoints and different assays used contributed to the lower efficacy. Second, we used SSA in selected patients with high GH levels, which may have led to poor outcomes. Furthermore, we did not find a significant difference in the treatment efficacy between CAB and SSA, although SSA was more potent than DA in reducing GH levels.

The low GH level before medication predicted the CAB and SSA treatment outcomes in the present study. However, we failed to find the cut-off values for pretreatment GH levels. Several studies have also reported that the baseline GH or IGF-1 levels before treatment are related to the efficacy of the treatment [27, 11]. The current guideline advised CAB use only in cases with mild-to-moderate diseases, or as a combination therapy with other drugs [5]. However, SSAs also showed a poor response in patients with acromegaly with high GH levels. The treatment duration was not associated with the therapeutic response in our study. Several studies suggested hyperprolactinemia or prolactin immunostaining as predictors of CAB response [19, 32]. However, similar to the observations in the recent meta-analysis as well as in the study by Sherlock et al. [11, 33], hyperprolactinemia did not affect the CAB treatment response in our study.

In treating acromegaly with CAB, about three times higher doses were required compared to that for prolactinomas, which evoked concerns for valvular heart diseases [20]. However, valvulopathy has not been found in patients receiving conventional CAB doses [34]. Therefore, we also did not find any patients with valvular heart diseases after taking CAB in our sample of patients with acromegaly. Periodic echocardiography must be recommended for patients receiving higher than conventional DA doses for a long time [5].

Our study has several strengths. We directly compared the efficacies of CAB, BCT, and SSAs in actual clinical practice. Although BCT users were dominant, the present study included a larger number of DA users than that included previous reports [11]. Simultaneously, we also investigated the predictive factors for the treatment outcomes. The treatment duration (median, 26.0 months)

Table 4  Logistic regression models of predictive factors for controlled disease (both GH <2.5 ng/mL and normal IGF-I) in patients with first- or second-line medical therapy

<table>
<thead>
<tr>
<th>Variables</th>
<th>First-line medical therapy</th>
<th>First- or second-line medical therapy</th>
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<tbody>
<tr>
<td></td>
<td>Unadjusted OR</td>
<td>Adjusted OR</td>
</tr>
<tr>
<td>CAB vs. BCT</td>
<td>6.67 (1.61–27.7)</td>
<td>4.54 (1.57–13.2)</td>
</tr>
<tr>
<td>SSA vs. BCT</td>
<td>4.00 (1.06–15.1)</td>
<td>2.96 (0.98–8.92)</td>
</tr>
<tr>
<td>SSA vs. CAB</td>
<td>0.53 (0.12–2.97)</td>
<td>0.65 (0.23–1.87)</td>
</tr>
<tr>
<td>Age at diagnosis (per years)</td>
<td>1.01 (0.97–1.05)</td>
<td>1.00 (0.97–1.04)</td>
</tr>
<tr>
<td>GH level before medication (per ng/mL)</td>
<td>0.97 (0.93–1.01)</td>
<td>0.95 (0.91–0.99)</td>
</tr>
<tr>
<td>IGF-I level before medication (per %)</td>
<td>0.99 (0.99–1.00)</td>
<td>0.99 (0.99–1.00)</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>0.59 (0.17–2.06)</td>
<td>0.60 (0.21–1.67)</td>
</tr>
<tr>
<td>Prior therapy of GKS or radiation</td>
<td>1.45 (0.50–4.20)</td>
<td>1.73 (0.74–4.04)</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>1.01 (0.99–1.02)</td>
<td>1.00 (0.99–1.02)</td>
</tr>
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</table>

Data are shown as odds ratios (95% confidence interval). Adjusted OR, adjusted for GH level before medication. BCT, bromocriptine; CAB, cabergoline; SSA, somatostatin analog. OR, odds ratio; GKS, gamma-knife surgery.
was much longer than that reported in previous studies, which ranged from 2.6 to 24 months [11].

Several limitations should be mentioned. First, as ours is a retrospective study, we were unable to randomize patients, and the baseline characteristics of patients were different among the three groups. Particularly, the SSA group was younger and had more severe diseases. We tried to adjust for the confounding factors but residual effects may exist. Owing to the small sample size, we further analyzed the efficacy of medication after including patients receiving second-line medication as well. Since the reasons for the choice of medication differed among the patients and baseline characteristics were heterogeneous, it is difficult to interpret the results from the combination of the first- and the second-line treatment to compare the different treatment modalities. In Korea, combination therapy such as that using both CAB and SSA was not applicable; therefore, the combination effect was not studied. The tumor diameter measurement after surgery was invisible or unavailable in more than half of patients, and we did not evaluate the effect of each drug on the tumor shrinkage. We included the patients with a history of prior gamma-knife surgery or radiation, which may have affected the treatment outcome. However, in the SSA group, more patients underwent gamma-knife surgery or radiation than in the CAB or BCT groups. In addition, gamma-knife surgery or radiation did not affect the treatment outcome (Supplementary Table 2). Furthermore, the IGF-1 assay used here did not presented the reference by sex differences. Due to lack of cases with T2-weighted MRI, we cannot provide the relationship between the MRI signal intensity and the SSA response. Lastly, we could not perform electron microscopic examination and could not describe the granulation pattern of adenomas.

In conclusion, in this retrospective study, we compared the efficacy of CAB, BCT, and SSAs in treating patients with acromegaly. According to our results, CAB was effective in treating acromegaly with a relative low cost. Lower pretreatment GH levels predicted better responses to DA or SSA, and hyperprolactinemia was not related with the treatment response. Our results may recommend CAB use for patients with acromegaly with low pretreatment GH levels, who are considering pharmacotherapy. Future studies are required to identify promising candidate drugs to actualize individualized therapy in patients with acromegaly.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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