GMJ 2024;35:433-437

DOI: http://dx.doi.org/10.12996/gmj.2024.4281

Long-Term Results of Cabergoline Add-on Long-Acting Somatostatin Analogue Therapy in Acromegaly Patients

Akromegali Hastalarında Uzun Etkili Somatostatin Analog Tedavisine Eklenen Kabergolin Tedavisinin Uzun Dönem Sonuçları

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ABSTRACT

Objective: To investigate the efficacy of the dopamine agonist cabergoline in uncontrolled acromegaly despite long-acting somatostatin analog (SSA).

Methods: Thirty-five patients with acromegaly who were followed up in the department of endocrinology and metabolism of our university were analyzed. Thirty-five patients with acromegaly who did not respond adequately to postoperative SSA and in whom cabergoline was added to the treatment were analyzed. Patients were retrospectively evaluated in terms of age, gender, insulin-like growth factor-1 (IGF-1) values before and after cabergoline, disease duration, treatment dose, adenoma size, growth hormone level, and prolactin staining on pathologic examination.

Results: Seventeen (48.6%) patients were female. The median age was 46.0 (41-53) years, and the median disease age was 10 (3-43) years. Twenty-eight (80.0%) were macroadenomas, 7 (20.0%) were microadenomas, and prolactin staining was observed in 10 (27.8%) cases. The IGF-1 level was 443 (346-628) ng/mL before cabergoline treatment and 27.4% decrease in IGF-1 was observed after treatment ($p<0.001$). There was no correlation between IGF-1 decrease and cabergoline dose. The change in IGF-1 was not correlated with tumor size and age but was correlated with pre-cabergoline IGF-1 level ($r=0.364$, $p=0.03$). 8 (22.9%) patients went into remission with cabergoline treatment. There was no difference in age, gender, tumor size, or pre-treatment IGF-1 levels between those who went into

ÖZ

Amaç: Uzun etkili somatostatin analoğuna (SSA) rağmen kontrol altına alınamayan akromegalide dopamin agonisti kabergolinin etkinliğini araştırmaktır.

Yöntemler: Üniversitemiz endokrinoloji ve metabolizma bölümünde takip edilen 35 akromegali hastası analiz edildi. Postoperatif dönemde kullandıkları SSA'ya yeterli yanıt vermeyen ve tedaviye kabergolin eklenen 35 akromegali hastası analiz edildi. Hastalar yaş, cinsiyet, kabergolin öncesi ve sonrası insülin benzeri büyüme faktörü-1 (IGF-1) değerleri, hastalık süresi, tedavi dozu, adenom boyutu, büyüme hormonu düzeyi ve patolojik incelemede prolaktin boyanması açısından retrospektif olarak değerlendirildi.

Bulgular: On yedi (%48,6) hasta kadındı. Ortanca yaş 46,0 (41-53) yıl ve ortanca hastalık yaşı 10 (3-43) yıldı. Hastaların 28'i (%80,0) makroadenom, 7'si (%20,0) mikroadenomdu ve 10 (%27,8) olguda prolaktin boyanması gözlendi. Kabergolin tedavisi öncesi IGF-1 düzeyi 443 (346-628) ng/mL iken tedavi sonrası IGF-1'de %27,4 azalma gözlendi ($p<0,001$). IGF-1 azalması ile kabergolin dozu arasında korelasyon yoktu. IGF-1'deki değişim tümör boyutu ve yaş ile korele değildi ancak kabergolin öncesi IGF-1 düzeyi ile korele idi ($r=0,364$, $p=0,03$). 8 (%22,9) hasta kabergolin tedavisi ile remisyona girmişti. Kabergolin tedavisi ile remisyona girenler ve girmeyenler arasında yaş, cinsiyet, tümör boyutu veya tedavi öncesi IGF-1 düzeyleri açısından fark yoktu. Bu 8 hasta incelendiğinde, takip süresi boyunca kabergolin tedavisine devam edildiği; bir hastada SSA tedavisi kesilerek, üç hastada SSA dozu

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Received/Geliş Tarihi: 31.08.2024
Accepted/Kabul Tarihi: 11.09.2024

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remission with cabergoline treatment and those who did not. When these 8 patients were analyzed, it was observed that cabergoline treatment was continued throughout the follow-up period; remission was maintained in one patient by discontinuing SSA treatment, in three patients by decreasing the SSA dose, in two patients without treatment change, and in two patients by changing the SSA preparation.

Conclusion: Cabergoline is used in the treatment of acromegaly due to its antiproliferative and proapoptotic effects on pituitary adenoma cells. The efficacy of cabergoline added to SSA treatment is controversial in the literature. In our study, remission was achieved in 22.9% and IGF-1 reduction was observed in 27.4% with cabergoline treatment in patients with inadequate response to SSA treatment. Cabergoline added to SSA is an effective treatment in terms of IGF-1 control. This effect may continue in the long-term.

Keywords: Acromegaly, cabergoline, somatostatin analog

ÖZ

azaltılarak, iki hastada tedavi değişikliği yapılmadan ve iki hastada SSA preparatı değiştirilerek remisyonun korunduğu gözlendi.

Sonuç: Kabergolin hipofiz adenom hücreleri üzerindeki antiproliferatif ve proapoptotik etkileri nedeniyle akromegali tedavisinde kullanılmaktadır. SSA tedavisine eklenen kabergolinin etkinliği literatürde tartışmalıdır. Çalışmamızda SSA tedavisine yetersiz yanıt veren hastalarda kabergolin tedavisi ile %22,9 oranında remisyon sağlanmış ve %27,4 oranında IGF-1 azalması gözlenmiştir. SSA'ya eklenen kabergolin IGF-1 kontrolü açısından etkili bir tedavidir. Bu etki uzun dönemde de devam edebilir.

Anahtar Sözcükler: Akromegali, kabergolin, somatostatin analoğu

INTRODUCTION

Acromegaly is a chronic disease caused by excessive secretion of growth hormone (GH), usually by a pituitary tumor. It is a disease that affects men and women equally, with a prevalence of 40 to 130 per million.

Although transsphenoidal surgery is the preferred first-line treatment for acromegaly (1), 20% of patients with microadenomas and 40-60% of patients with macroadenomas cannot be cured only by surgery and require adjuvant medical therapy (2). Pharmacological treatments; including long-acting somatostatin analogs (SSA), dopamine agonists, and GH receptor antagonists, have gained importance in providing biochemical and symptomatic control of the disease (3).

SSAs are considered the first choice for the medical treatment of acromegaly and can normalize insulin-like growth factor-1 (IGF-1) levels in approximately 50% of patients (4). However, IGF-1 normalization is not achieved in at least 35% of patients, suggesting resistance to SSAs (2). In addition, in some patients, drug compliance may be poor because of side effects or injection-related difficulties (5).

Pegvisomant (PEG), which acts as a GH receptor antagonist, either alone or when added to SSA, normalizes IGF-1 levels in approximately 97% of patients but does not cause tumor shrinkage (1). Regular monitoring of liver enzyme levels, intermittent changes in injection sites, and skin examination for lipohypertrophy or rashes are important in patients treated with this drug (6). The need for daily injections and its high cost limit the use of PEG (7,8).

Cabergoline is an ergot-derived dopamine D2 receptor agonist that can be used for the medical treatment of acromegaly. The antiproliferative and proapoptotic effects on pituitary tumor cells have been observed in various studies. Cabergoline can be used alone or as an add-on therapy in patients who are partially resistant to SSA or who are not fully controlled with maximum dose PEG. It has been shown to normalize plasma IGF-1 levels in up to 39% of patients with acromegaly during monotherapy. In addition, the convenience of oral administration, better compliance, and lower economic costs compared with SSA and PEG make cabergoline an attractive option for acromegalic patients who often need long-lasting medical therapy to achieve disease control (9).

As data on the beneficial effects of adding cabergoline to the medical regimen in acromegalic patients uncontrolled with long-acting SSAs are still limited (1); the aim of this study was to examine the efficacy of dopamine agonist cabergoline treatment in uncontrolled acromegaly despite the long-acting SSA and to observe the long-term results of this treatment.

MATERIALS AND METHODS

Permission was received for our research from Gazi University Faculty of Medicine Ethics Committee (approval number: 597, date: 28.06.2021). Among the patients with acromegaly who were followed up in the Gazi University Faculty of Medicine, Department of Endocrinology and Metabolism between January 1, 2005, and February 1, 2020; thirty-five cases, in which cabergoline was added to the treatment because of insufficient response to SSA were analyzed retrospectively. The patients were evaluated in terms of age, gender, IGF-1 values before and after cabergoline treatment, disease duration, treatment dose, adenoma size, GH level, and prolactin staining on pathological examination. Since the normal value range for IGF-1 level is a parameter that changes with age, the ratio of "patient's IGF-1 value/upper limit of normal for age-specific IGF-1" was used in the statistical calculation. In the evaluation after cabergoline treatment, control IGF-1 measurements at the 3rd month after treatment were used.

Patients who did not use SSA and were followed up only with cabergoline, those who underwent simultaneous SSA dose changes with the addition of cabergoline, those who added PEG concurrently with cabergoline, and those who did not have follow-up data were excluded from the study.

Statistical Analysis

In our study, statistical analyses will be performed using SPSS for Windows Version 22' program. Frequencies for the variables in the categorized data type (qualitative) and the mean ± standard deviation, if suitable for the normal distribution, for the variables in the numerical data type (quantitative) and median (minimum-maximum) values if not suitable for the normal distribution, were specified. Whether the variables fit the normal distribution or not was evaluated with the Kolmogorov-Smirnov test. Parametric tests (Independent sample t-test) were used for variables that matched

the normal distribution, and non-parametric tests (chi-square, Mann-Whitney U test) were used for those that did not. The Spearman correlation test was used for the correlation between continuous variables. The statistical significance value of this study was accepted as p≤0.05.

RESULTS

Seventeen (48.6%) patients were women. The median age was 46.0 (41-53) years, and the disease age was 10 (3-43) years. The follow-up period for cabergoline treatment was 6.0 (1-15) years. There were macroadenomas in 28 (80.0%) patients, microadenomas in 7 (20.0%) patients, and prolactin staining in addition to GH was observed in pathological samples from 10 (28.5%) patients. 20 (57.1%) patients had a history of gamma-knife therapy before cabergoline treatment. The maximum cabergoline dose was 1.50 mg/week (1-5 mg/week) (Table 1).

The median IGF-1 level was 443 ng/mL before cabergoline treatment, it was 308 ng/mL after cabergoline. A 27.4% decrease in IGF-1 levels was observed after cabergoline treatment (p<0.001). Although the upper limit of normal ratio for IGF-1/IGF-1 before cabergoline was 1.53 (1.10-5.30), it was found to be 1.16 (0.20-3.60) after cabergoline (Table 2).

Although the change in IGF-1 levels was positively correlated with pre-cabergoline IGF-1 level (P=0.364, p=0.03), no correlation was found between tumor size, age, and cabergoline dose.

Eight (22.9%) patients achieved normal IGF-1 levels following cabergoline treatment. No difference was observed between patients with normal IGF-1 levels who received cabergoline treatment and those with high IGF-1 levels in terms of age, sex, tumor size, disease duration, duration of follow-up with cabergoline treatment, prolactin staining, and history of gamma-knife before cabergoline.

Table 1. General characteristics of patients

Age (year)*	46.0 (27-69)
Disease duration (year)*	10.0 (3-43)
Cabergolin treatment duration (year)*	6.0 (1-15)
Maximum CAB dose (mg/week)	1.5 (1-5)
Macroadenoma, n (%)	28 (80)
Prolactin staining percentage, (%)	
Positive	10 (28.5)
Negative	16 (45.8)
Unknown	9 (25.7)
Gamma knife therapy before CAB, n (%)	20 (57.1)

*Median (minimum-maximum). CAB: Cabergoline.

In 8 patients with normal IGF-1 levels after cabergoline treatment, the maximum cabergoline dose was 1.00 (1-2) mg/week, and the percent IGF-1 change was -47.41 (-81.92/-26.33) with cabergoline treatment. In this patient group, the upper limit of normal ratio for IGF-1/IGF-1 before cabergoline was 1.31 (1.10-1.67), whereas the upper limit of normal ratio for IGF-1/IGF-1 after cabergoline was 0.79 (0.20-1.00) was determined (p<0.01).

In 27 patients with high IGF-1 levels after cabergoline therapy, the maximum cabergoline dose was 2.00 (1-5) mg/week; upper limit of normal for pre-cabergoline IGF-1/IGF-1 was 1.65 (1.10-5.30); upper limit of normal for IGF-1/IGF-1 after cabergoline is 1.37 (1.02-3.60); The percent change in IGF-1 with cabergoline treatment was -18.02 (-75.65/21.01). There was a statistically significant difference between the two patient groups with normal IGF-1 and high IGF-1 levels after cabergoline treatment in terms of the maximum dose of cabergoline and the percentage of change in IGF-1 levels with cabergoline therapy (p=0.050; p=0.019) (Table 3).

A statistically significant difference was observed between the upper limit of normal for IGF-1/IGF-1 before cabergoline and the upper limit of normal for IGF-1/IGF-1 after cabergoline between these two groups (p=0.001; p<0.01) (Table 2).

After cabergoline therapy, cabergoline therapy was continued for a median follow-up of 4 years (1-8 years) in 8 patients with normal IGF-1 levels; It was observed that the normal IGF-1 level was maintained by discontinuing SSA treatment in one patient, decreasing the SSA dose in three, without changing the treatment in two, and changing the SSA preparation in two.

DISCUSSION

Long-term medical treatment is important for patients with acromegaly when an adequate response cannot be achieved with surgical treatment. Although SSA is preferred in the first line, SSA unresponsiveness can be observed even when the maximum dose is reached (10). Since the late 1990s, studies have been carried out to add cabergoline to SSA treatment.

In studies on cabergoline treatment added to SSA, IGF-1 normalization was found to be between 42% and 44% at 6-12 months follow-up (11,12). Studies have shown that this combination is most effective in patients with mildly elevated IGF-1 levels (13). In our study, the upper limit of the normal ratio for IGF-1/IGF-1 was 1.31 (1.10-1.67) times in patients with normal IGF-1 levels under cabergoline treatment, whereas this ratio was 1.65 (1.10-5.30) times in patients with high IGF-1 levels. In light of this information, we believe that cabergoline treatment may be more effective in patients with mild to moderate IGF-1 levels in the postoperative period. There are also data in this direction in the literature (9).

In longer (18-24 months) follow-up periods, normalization of IGF-1 levels were observed at rates ranging from 37% to 40% (1,14). Abs et al. (15) treated 64 patients with acromegaly for 40 months and

Table 2. IGF and IGF-1/IGF-1 ULN before and after CAB

	Before CAB	After CAB	p
IGF-1 (ng/mL)*	443.0 (265-1607)	308.0 (52-1091)	<0.01
IGF-1/IGF-1 ULN*	1.5 (1.1-5.3)	1.2 (0.2-3.6)	<0.01

*Median (minimum-maximum). IGF-1: Insulin-like growth factor 1, ULN: Upper limit of normal, CAB: Cabergoline.

Table 3. Clinical and laboratory parameters between normal and high IGF-1 levels after CAB

	Normal IGF-1 after CAB, (n=8)	High IGF-1 after CAB, (n=27)	
Female, n (%)	6 (75)	11 (40.7)	0.12
Age (year)*	47.0 (34-64)	46.0 (27-69)	0.69
Disease duration (year)*	8.5 (3-43)	10.5 (4-36)	0.813
Follow-up period (year):	4.0 (1-8)	6.0 (1-15)	0.173
Macroadenoma, n (%)	7 (87.5)	21(77.8)	1.00
Prolactin staining percentagen (%)			
Positive	2 (25)	8 (29.6)	1.00
Negative	4 (50)	12 (44.4)	
Unknown	2 (25)	7 (26.0)	
Gamma Knife therapy before CAB, n (%)	4 (50)	16 (59.3)	0.70
Max CAB dose (mg/week)	1.0 (1.0-2.0)	2.0 (1.0-5.0)	0.05
IGF-1 before CAB*	335 (265- 418)	500 (272-1607)	**<0.001**
IGF-1 after CAB*	177 (52-230)	353 (262-1091)	**<0.001**
IGF-1/IGF-1 ULN before CAB	1.31 (1.10-1.67)	1.65 (1.10-5.30)	**<0.001**
IGF-1/IGF-1 ULN after CAB	0.79 (0.20-1.00)	1.37 (1.02-3.60)	**<0.001**
IGF decrease after CAB (%)	-47.4 (-81.9/-26.3)	-18.0 (-75.7/-21.0)	**0.02**

*Median (minimum-maximum). IGF-1: Insulin-like growth factor 1, CAB: Cabergoline, ULN: Upper limit of normal.

found that IGF-1 reached normal levels in 39% of the patients after cabergoline use (at doses ranging from 1.0-3.5 mg per week). In our study, there was 30.5% decrease in IGF levels after CAB therapy in patients already on SSA treatment after 6.0 (1-15) years follow-up period. 22.9% of patients achieved normal IGF levels with CAB therapy.

One of our patients with normal IGF-1 levels after cabergoline treatment was discontinued from SSA treatment and was followed up only under cabergoline treatment. In 3 patients, the current SSA dose could be reduced. In 2 patients, we continue to follow-up with normal IGF-1 levels under cabergoline treatment without SSA dose change during the 4 and 8-year follow-up periods. In 2 patients, while they were followed up at normal IGF-1 level with cabergoline during the 2-year follow-up period, we observed that the IGF-1 level returned to normal levels by making changes in the SSA preparation due to the increasing trend of IGF-1 level after 2 years. Based on the present data, it can be concluded that the normal IGF-1 level obtained under cabergoline treatment can be maintained over the long term.

Study Limitations

Our study has some limitations. First, this was a retrospective designed study. The small sample size prevented us from drawing definite conclusions. Since the patients were normoprolactinemic, the correlation between cabergoline treatment and prolactin levels could not be evaluated.

CONCLUSION

In our study, in patients who did not respond adequately to SSA treatment, normalization of IGF-1 level was reached in 22.9% and IGF-1 reduction was observed in 27.4% with cabergoline treatment. Cabergoline added to SSA may be an effective treatment for the control of acromegaly in patients with moderately high IGF-1 levels. We believe that this effect may continue in the long term.

Ethics

Ethics Committee Approval: Permission was received for our research from Gazi University Faculty of Medicine Ethics Committee (approval number: 597, date: 28.06.2021).

Informed Consent: Retrospective study.

Authorship Contributions

Concept: M.E.Y., G.B.K., M.C., A.B., E.Ç., M.A.İ., E.C., A.P., E.T.C., A.E.A., M.A., F.B.T., M.A.K., İ.Y., Design: M.E.Y., G.B.K., M.C., A.B., E.Ç., M.A.İ., E.C., A.P., E.T.C., A.E.A., M.A., F.B.T., M.A.K., İ.Y., Supervision: M.E.Y., G.B.K., M.C., A.B., E.Ç., M.A.İ., E.C., A.P., E.T.C., A.E.A., M.A., F.B.T., M.A.K., İ.Y., Resources: M.E.Y., G.B.K., M.C., A.B., E.Ç., M.A.İ., E.C., A.P., E.T.C., A.E.A., M.A., F.B.T., M.A.K., İ.Y., Material: M.E.Y., G.B.K., M.C., A.B., E.Ç., M.A.İ., E.C., A.P., E.T.C., A.E.A., M.A., F.B.T., M.A.K., İ.Y., Data Collection or Processing: M.E.Y., G.B.K., M.C., A.B., E.Ç., M.A.İ., E.C., A.P., E.T.C., A.E.A., M.A., F.B.T., M.A.K., İ.Y., Analysis or Interpretation: M.E.Y., G.B.K., M.C., A.B., E.Ç., M.A.İ., E.C., A.P., E.T.C., A.E.A., M.A., F.B.T., M.A.K., İ.Y., Literature Search: M.E.Y., G.B.K., M.C., A.B., E.Ç., M.A.İ., E.C., A.P., E.T.C., A.E.A., M.A., F.B.T., M.A.K., İ.Y., Writing: M.E.Y., G.B.K., M.C., A.B., E.Ç., M.A.İ., E.C., A.P., E.T.C., A.E.A., M.A., F.B.T., M.A.K., İ.Y., Critical Review: M.E.Y., G.B.K., M.C., A.B., E.Ç., M.A.İ., E.C., A.P., E.T.C., A.E.A., M.A., F.B.T., M.A.K., İ.Y., Other: M.E.Y., G.B.K., M.C., A.B., E.Ç., M.A.İ., E.C., A.P., E.T.C., A.E.A., M.A., F.B.T., M.A.K., İ.Y.

Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study received no financial support.

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