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PROS AND CONS IN ENDOCRINE PRACTICE

Cabergoline treatment in acromegaly: pros

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Abstract Cabergoline is an ergot-derived dopamine D2 receptor agonist which may be effective for the medical management of acromegaly. Its efficacy in reducing growth hormone and IGF-I levels, as well as its antiproliferative and pro-apoptotic effects on pituitary tumor cells, has been observed in several studies. Cabergoline may be used alone or as an add-on therapy to patients who are partially resistant to somatostatin analogs (SSA), or who do not achieve complete control with maximum doses of pegvisomant (PEG). Additionally, the convenience of its oral administration, allowing better compliance, and its lower economic cost, in comparison with SSA and PEG, favor cabergoline as an attractive option for acromegalic patients, who frequently require long-life medical treatment to achieve disease control. The few adverse events observed with prolonged DA therapy, mainly regarding cardiac valve disease, are not frequent at the doses generally used in acromegaly.

Keywords Acromegaly · Cabergoline · Medical treatment · Acromegaly treatment · Cabergoline treatment

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Shortly after the observations that growth hormone (GH) paradoxically decreased after dopamine [1, 2], bromocriptine became the first available medical treatment for acromegaly. Symptomatic and objective clinical improvement was initially described [3, 4], but incomplete biochemical responses, poor patient tolerance to the high doses required, and the need for multiple daily administration limited its relevance [5].

Cabergoline, an ergot-derived dopamine agonist (DA) with high affinity for dopamine D2 receptors and low affinity for dopamine D1, α1- and α2-adrenergic, and 5-HT1- and 5-HT2-serotonin receptors, is more potent, long lasting and better tolerated than bromocriptine [6, 7], and may exert antiproliferative and pro-apoptotic effects, not only in prolactinomas, but also in some other pituitary adenomas [8]. Since a considerable number of acromegalic patients require long-life medical treatment to achieve disease control, cabergoline has two main advantages: (1) convenience of oral administration, allowing better compliance, and (2) its lower economic cost, in comparison with somatostatin analogs (SSA) and pegvisomant (PEG).

Cabergoline used as monotherapy

In the first studies, which included a small number of patients, short follow-up, and various doses [9, 10], biochemical efficacy of cabergoline was uncertain. Later, a study by Colao et al. [11] in 11 patients treated with cabergoline 1–2 mg/week for 6 months observed a GH suppression of 48.5 % during chronic treatment, as well as improvement in acromegalic clinical features, with no side effects. In a similar study of ten patients in which higher doses were used (1 mg twice weekly to 0.5 mg daily) during 4 months, seven individuals showed reductions in

GH and IGF-1 levels to less than 33 and 67 % of basal values, respectively [12].

Subsequent studies with a larger number of patients have highlighted the usefulness of cabergoline in acromegaly. For instance, a single-center, prospective study including 18 acromegalic patients treated with cabergoline (1–3.5 mg per week) for 6 months showed a percentage GH decrease of 41.9 %, and in 44 % of patients insulin-like growth factor-I (IGF-I) levels were suppressed below 50 % of baseline. GH normalization was achieved in 27 % of patients, IGF-I normalization was also reached in 27 % of the series, and an overall biochemical remission, with normality of both GH and IGF-I levels, was observed in 22 % of cases. Shrinkage of tumor size was observed in the three cases whose pituitary magnetic resonance imaging was repeated during follow-up [13].

In a larger, multicenter, prospective, and open-label study carried out in Belgium [14] with 64 unselected acromegalic patients, cabergoline therapy was started at 0.5 mg twice/week and was gradually increased during 3–40 months until normalization of IGF-I levels, occurrence of unacceptable side effects, or a maximal weekly dose of 3.5 mg (7.0 mg in one case) was reached. Plasma IGF-I levels were reduced below 300 μg/L in 39 % of patients, and a decrease in GH levels below 2 μg/L was observed in 46 % of patients. Response to cabergoline treatment was better in patients whose pituitary adenoma co-secreted GH and prolactin (PRL), but was less noteworthy in those cases who had higher baseline GH (>20 μg/L) and IGF-I (>750 μg/L) levels. Pituitary magnetic resonance imaging follow-up studies were performed in 21 cases (four microadenomas and 17 macroadenomas); a significant decrease in tumor size was evidenced in one microadenoma and in 12 macroadenomas, with five cases achieving a mass reduction greater than 50 %, and, again, a better response was observed in those tumors with GH/PRL co-secretion. Cabergoline was well tolerated, and only two patients (3 %) stopped treatment because of side effects. Other small studies described similar outcomes [15, 16].

Despite these promising results, cabergoline has sometimes been considered "insufficiently effective" for the medical management of acromegaly. The underlying reasons probably concern the disappointing results from the first above-mentioned small studies, previous unsatisfactory experience with bromocriptine, the increasing availability and demonstration of efficacy of SSA, and findings suggesting that cabergoline effects wane with time [17].

A recent meta-analysis by Sandret et al. [18] reviewed all the available studies of cabergoline therapy for acromegaly published up to 2009 in four databases. Cabergoline was used as a single-agent therapy in ten trials, with a total of 160 patients. Mean reductions of GH and IGF-I levels were 47 and 33 %, respectively, and normalization of GH (<2.5 ng/mL) and IGF-I was obtained in 48 and 34 % of cases, respectively. Multivariate analysis evidenced that GH response was related to baseline GH concentration and cabergoline dose. Similarly, the decline in IGF-I was related to baseline IGF-I concentrations, treatment duration and baseline PRL levels, and with a trend toward a relation with cabergoline doses. So, overall, this meta-analysis suggested that cabergoline used as monotherapy could achieve normalization of IGF-I levels in one-third of patients with acromegaly, and no tendency to treatment escape or tachyphylaxis was identified [14, 18]. Adenoma shrinkage was also observed in about one-third of patients [10, 15, 19], and prolonged remission was anecdotally communicated [20].

Cabergoline added to ongoing SSA therapy

Few studies have evaluated the outcomes of SSAs and cabergoline combination therapy in acromegalic patients [21–25], but they have all reached similar findings. The combined regime obtained a greater suppression of GH and IGF-I levels than monotherapy of either drug alone [22, 23], with good tolerance [23], and improvement in patients' compliance [21]. A further increase in cabergoline doses could potentially improve efficacy of treatment even more [23, 26].

The above-mentioned meta-analysis by Sandret et al. [18] reviewed five studies which used cabergoline as an add-on therapy to patients with partial response to SSA monotherapy. Mean duration of combined treatment was shorter than with monotherapy of either drug, although mean doses of cabergoline were similar to when it was used alone. Mean reductions of IGF-I and GH serum concentrations were 30 and 19 %, respectively, and a total of 52 % of patients achieved normalization of IGF-I levels. In multivariate analysis, the decline in IGF-I levels was related to baseline IGF-I, but not to cabergoline dosages, duration of treatment, nor to baseline PRL concentrations. Similarly, mean GH concentration fell significantly when cabergoline was added to SSA and, again, in multivariate analysis, changes in GH correlated with baseline GH levels.

Overall, combination therapy allowed a further significant improvement in biochemical control in comparison with SSA monotherapy, and almost 50 % of patients with only partial response to SSA alone achieved normalization when cabergoline was added. The amplitude of efficacy of cabergoline has been observed to depend on baseline IGF-I levels. However, some patients with very high levels of IGF-I still achieve normalization; so, it has been suggested that cabergoline might be worth trying in all acromegalic patients who require medical treatment [18].

Regarding tumor histology and immunohistochemistry some authors have acknowledged a better efficacy of the combination of cabergoline and SSA in the setting of GH/PRL co-secreting adenomas [27], suggesting PRL levels as predictors of responsiveness. However, others have found no such predictive value, and advocate for a cabergoline trial in all SSA partially resistant acromegalic patients, irrespective of their pituitary tumor phenotype [16, 22, 23, 28]. Even though the secretory response may not be influenced by the mixed (PRL/GH) nature of the adenoma, the tumor response, i.e., its size, did show a better reduction when PRL levels were elevated [10–12, 14, 29].

Cabergoline as an add-on therapy to PEG

Experimental data suggest that response to cabergoline is preserved in acromegalic patients treated with the GH-receptor antagonist PEG [30]. The anti-secretory and anti-proliferative effects of cabergoline could complement the action of PEG [8] and improve biochemical and tumor control [18]. Furthermore, this combination could enable the use of lower doses and, therefore, reduce costs. In fact, this combined scheme has been observed to be followed in around 10 % of acromegalic patients included in the ACROSTUDY [31].

A multicenter, open-label, prospective clinical trial recruited 24 patients [32] and observed that although cabergoline alone did not significantly reduce IGF-I levels with doses of up to 0.5 mg/day, after 12 weeks of treatment with the combination of cabergoline and low-dose PEG (10 mg/day), IGF-I levels did fall significantly, and 68 % of patients achieved normalization. Then, when cabergoline was withdrawn and PEG monotherapy was continued for 12 more weeks, only 26 % of patients maintained normal IGF-I levels.

We recently conducted a retrospective observational cross-sectional study [33] of 14 acromegalic patients who were partially resistant to SSA and were on PEG monotherapy. Cabergoline was added because of the presence of persistent mildly increased IGF-I. We observed that PEG + cabergoline normalized IGF-I levels in 28 % of patients and decreased IGF-I in 64 %. A better response to this combined treatment was associated with baseline IGF-I levels below 160 % of the ULN, female gender, lower body weight, higher baseline PRL concentrations, and positive PRL immunostaining.

In summary, recent studies have shown interesting results for the clinical practice setting regarding the possibility of combining PEG and cabergoline as an alternative effective option to allow further improvement in acromegalic patients. Biochemical control may be achieved in >50 % of patients following this combined scheme, even in patients who were not previously controlled with PEG monotherapy at maximum doses, and with no significant adverse events [32–34].

Cabergoline and fibrotic complications

The use of DA has sometimes been limited because of the development of mild side effects, such as nausea, constipation, orthostasis, headache, and mood disturbance. One additional concern has been its association to heart valve alterations in patients with Parkinson's disease [35]. Binding to 5-HT(2B) cardiac receptors has been implicated in its pathogenesis, but this does not occur in all patients and no susceptibility factors have been described yet.

The relevance of this adverse effect in patients with acromegaly is still unclear, because doses used in this setting are significantly lower than those used in Parkinson's disease. Valve complications have not been found in patients receiving conventional DA doses for pituitary tumors [36–38]. However, prudency seems reasonable, mainly because doses of cabergoline in acromegalic patients may be higher than the ones used in patients with prolactinomas. Monitoring of patients receiving higher than conventional DA doses for prolonged periods of time with periodic echocardiography should be warranted, and this would serve as a simple and low-cost approach to confidently rule out any potential cardiac fibrotic complications. Nevertheless, the possible presence of previous cardiac disease should also be taken into account.

Table 1 Summary of the main issues regarding the role of cabergoline for the medical treatment of acromegaly

Cabergoline	Monotherapy	↓ GH/IGF1 ≈ 40 %
General caveats: consider in modest disease and maybe if ↑PRL		Normalization GH/IGF1 ≈ 30 %
		Tumor shrinkage possible
	+ SSAs	↓ GH/IGF1 ≈ 40 %
		Normalization GH/IGF1 ≈ 50 %
		Useful if partially response to SSAs or if SSA poorly tolerated
	+ PEG	↓ GH/IGF1 ≈ 60–70 %
		Normalization GH/IGF1 ≈ 20–30 %

↑ increased, ↓ decreases, ≈ approximately, + added therapy

PRL prolactin, *SSA* somatostatin analogs, *PEG* pegvisomant, *GH* growth hormone, *IGF-I* insulin-like growth factor-I

Conclusions

Cabergoline was approved for the treatment of hyperprolactinemia after SSAs were already an established alternative for the medical management of acromegaly. The main criticism to cabergoline is the lack of randomized controlled trials in the specific setting of acromegaly; so, current guidelines [39] address DA therapy in third place, following SSA and PEG.

However, the efficacy of cabergoline to reduce GH and IGF-I levels has been observed in several studies, both as monotherapy and in combination schemes, and it has been further remarked that its potency increases with treatment duration. Also, its oral administration and its lower cost in comparison with other treatment options favor its use in every-day clinical practice, especially now that cost issues are a major concern.

The predictive value of concomitant hyperprolactinemia or PRL immunostaining in tumor histology for biochemical control is currently controversial and should not be regarded as a definitive parameter to consider or disregard cabergoline administration. Nevertheless, hyperprolactinemia may in fact be a predictive factor of tumor shrinkage with adjunctive cabergoline treatment. The few adverse events observed with prolonged DA therapy, mainly regarding cardiac valve disease, are not frequent at the doses generally used in acromegaly. Prevention of these unusual complications may be easily monitored with non-invasive and low-cost techniques such as periodic ultrasonographic evaluations.

In conclusion, cabergoline may be an alternative medical approach for persistent acromegaly (Table 1), especially in the postoperative setting, when mild or moderate elevations of GH and IGF-I (<1.5 de ULN) are still observed.

Conflict of interest The authors declare no conflict of interest.

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