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PROS AND CONS IN ENDOCRINE PRACTICE

Cabergoline treatment in acromegaly: cons

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Abstract Many options are available for the treatment of acromegaly, including surgery, radiotherapy, and medical treatment. Cabergoline (CAB), a dopamine agonist with high affinity for dopamine receptor type 2, has been used both in monotherapy and in conjunction with somatostatin analogs (SSAs). Although it is administered orally and has a relatively lower-cost in comparison with SSAs, few studies have demonstrated its usefulness, there is a lack of randomized-controlled trials and other drugs (SSAs and pegvisomant) with more data in the literature are available; these issues are the main drawbacks of adopting CAB for the treatment of acromegaly.

Keywords Acromegaly · Dopamine agonists · Cabergoline · Treatment

Introduction

The treatment of acromegaly has evolved considerably in the last few decades [1]. In addition to more modern surgery and radiotherapy techniques, new medical therapies have been added to the treatment arsenal [1, 2]. Three drug classes are available for the treatment of acromegaly: dopamine agonists (DA), somatostatin analogs (SSAs), and antagonists of the growth hormone (GH) receptor [1]. DA were the first class of drugs used for the treatment of acromegaly, but bromocriptine, the initial drug prescribed, is no longer recommended for its treatment because of its low efficacy (achieving only ~10 % control over the disease) [1]. Cabergoline (CAB), a DA with higher affinity for dopamine receptor type 2 and, therefore, with higher theoretical efficacy and fewer side effects, has since been proposed for the medical treatment of acromegaly [3–6]. However, little evidence is available in the literature regarding its use in acromegaly. In this review, we will discuss the use of CAB in the treatment of acromegaly, emphasizing the paucity of clinical data in the literature, especially the absence of randomized-controlled clinical trials and the availability of other, more established options for treatment.

Cabergoline as a monotherapy

CAB as the primary treatment of acromegaly

Surgery remains the primary therapy in patients harboring tumors with a high likelihood of surgical cure (e.g., microadenomas or intrasellar macroadenomas) or presenting with visual impairment due to tumor compression of the optic chiasm [1]. In the cases of intrasellar adenomas, cure of acromegaly can be achieved in ~70 % of the patients when surgery is performed by a skilled neurosurgeon; such surgery is associated with low morbidity and very low mortality rates (0.1 %) [7]. However, for patients harboring

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tumors with extrasellar invasion, who therefore have a low chance of experiencing a surgical cure, medical treatment can be the first option of therapy [1]. In this situation, SSA administration is considered the primary medical therapy [1, 2]. In a critical analysis of the literature, primary treatment with the SSA octreotide was analyzed in 266 patients; normalization of the GH levels was obtained in 53 % of the patients, and normalization of insulin-like growth factor type I (IGF-I) was obtained in 54 % of the cases [8]. In addition, tumor shrinkage of more than 10 % was observed in 87 % of the patients, and shrinkage of more than 50 % was observed in 43 % of the patients [8]. However, it is important to emphasize that in this critical analysis, there was a high heterogeneity of studies and in many studies there was pre-selection of patients. The control rates in prospective clinical trials and in "real life" data from reference centers are lower [9–13]. In the prospective multicenter studies with both octreotide LAR and lanreotide autogel, biochemical control of acromegaly was obtained in about 30 % of the patients, and tumor shrinkage was observed in ~75 % of the patients [10, 11]. SSAs have also been compared with surgery as the primary treatment for acromegaly in a randomized-controlled trial including 101 patients; this trial showed that the two interventions do not differ in terms of biochemical and tumor control outcomes [14]. In all of these prospective trials with SSA, the drugs showed good safety profiles with no serious adverse events. In contrast, there are no randomized-controlled studies comparing CAB with either surgery or SSA as a primary treatment of acromegaly. Considering the prospective studies that evaluated CAB as a monotherapy, only 29 patients were treated with CAB as first-line therapy, but individual-level information regarding these patients was lacking [15]. Therefore, due to a lack of evidence, CAB should not be recommended as a primary medical therapy for acromegaly and instead should be eschewed in favor of surgery and SSA, as there is more evidence of the biochemical efficacy of these other two approaches, as well as evidence for their safety in this setting.

CAB as an adjuvant therapy

Surgery is the treatment modality indicated as a primary treatment that can lead to the cure of acromegaly. However, because a considerable percentage of patients harbor invasive macroadenomas, many patients will need adjuvant therapy [1, 7]. In the critical analysis that evaluated SSA, a large number of patients were evaluated regarding adjuvant treatment (612 patients on octreotide LAR therapy), and normalization of IGF-I was observed in 67 % of these patients [8]. Even after excluding pre-selected patients, normalization of IGF-I was observed in 63 % of the patients [8]. In the randomized-controlled trial cited previously, a total of 59 patients were treated with lanreotide autogel as an adjuvant therapy, and the percentage of normalization of both GH and IGF-I was 51 % [11].

The use of CAB as a monotherapy after unsuccessful surgery has only been evaluated in small series, many with pre-selection of patients and with short follow-up periods [3–5, 15–17]. In a recent meta-analysis, the efficacy of CAB as a monotherapy was evaluated, and only 10 studies including a total of 160 patients were found in the literature [15]. None of them was a randomized or placebo-controlled study. The mean duration of treatment was 10.8 months, and normalization of IGF-I was observed in 34 % of the patients [15]. In a recent retrospective series in the literature, CAB treatment was reported as a monotherapy for 353 patients, with achievement of normal GH and age-adjusted IGF-I levels for 20 % of the patients [18]. In this same series, a total of 923 patients were treated with SSA, and normalization of both GH and IGF-I levels was observed for 39 % of the patients [18].

There are no studies specifically evaluating the reduction in tumor volume with CAB in acromegaly. Tumor volume outcome has seldom been reported in studies; this issue has only been evaluated in 49 patients, with tumor reduction being observed in only 17 (34 %). Moreover, definitions of tumor reduction have been heterogeneous across studies [15]. In contrast, tumor reduction is observed in 53 % of the patients during treatment with octreotide, and this number increases to 66 % when considering only studies that used octreotide LAR as the treatment drug, with a mean tumor reduction of 51 % [19]. In studies with lanreotide autogel, the percentage of tumor shrinkage was similar (71 %) [20].

Considering the above evidence, SSAs have greater efficacy in terms of both tumor shrinkage and biochemical control in comparison with CAB and are, therefore, recommended as the first choice medical therapy for the treatment of acromegaly patients not cured by surgery [1, 21]. In addition, a much better experience is reported in the literature when using SSA with respect to efficacy and long-term results [1, 2, 21]. Exceptions are the cases of mildly elevated GH and IGF-I levels and those of prolactin co-secretion (~30 % of the tumors) when CAB monotherapy may have a better efficacy than the SSA, and therefore, can be considered as the first option of therapy [3, 15].

CAB in conjunction with other drugs

CAB in conjunction with SSAs

As previously reported, SSAs are the first-line medical treatments for acromegaly; however, a proportion of

Table 1 Studies evaluating the combination of CAB and SSAs

Studies (first author, publication year)	Study design	Sample size	Maximum follow-up (months)	Number of patients achieving normal GH and IGF-I levels (%)	Number of patients achieving normal IGF-I levels (%)
Marzullo (1999) [24]	Prospective	10	3	NA	5 (50)
Cozzi (2004) [22]	Prospective	19	7	3 (16)	8 (42)
Selvarajah (2005) [25]	Retrospective	4	14	1 (25)	2 (50)
Gatta (2005) [6]	Retrospective	10	55	4 (40)	6 (60)
Jallad (2009) [23]	Prospective	34	6	17 (50)	19 (56)
Mattar (2010) [27]	Prospective	19	18	NA	7 (37)
Vilar (2011) [26]	Prospective	52	24	15 (29)	21 (40)
Suda (2013) [28]	Retrospective	10	6	NA	3 (30)
Total		158	24	40 (34)	71 (45)

GH growth hormone, *IGF-I* insulin-like growth factor type I, *NA* not available

patients remain with active disease during SSA therapy. Therefore, the addition of CAB to the treatment of these patients has been proposed and has been reported in eight studies (Table 1); none of these studies was a randomized or placebo-controlled trial [6, 22–28]. The maximal duration of follow-up was 24 months. A total of 158 patients were included, and normalization of IGF-I levels was observed in 71 patients (45 %); normalization of both GH and IGF-I levels was observed in 34 % of the patients. However, in those patients with mildly elevated GH and IGF-I levels (especially below 2.2 times the upper limit of the IGF-I normal range and below 4.0–5.0 ng/mL of GH), there was a superior response, and CAB was shown to be a good treatment option [26, 27]. There is no study specifically addressing the outcome of tumor volume using a combination therapy.

Although a percentage of patients' cases can be controlled with the addition of CAB to SSA therapy, the addition of pegvisomant, a GH receptor antagonist, has also been reported in the literature, with much higher efficacy [29–31]. The association of other drugs with PEG in patients resistant to the treatment with the former is based in the knowledge that the shrinkage effects of SSA or CAB may occur in some patients independent of the tight biochemical control, probably depending on the SSTR expression profile of the tumor for the SSA therapy [32, 33]. The combination of pegvisomant and an SSA led to the normalization of IGF-I levels in 90 % of the cases studied [29, 31]. In addition, tumor shrinkage of greater than 20 % was reported for 19 % of the patients with this combination, mainly reflecting the action of the SSA [29]. Therefore, in those patients not controlled with SSA after surgery, in the absence of tumor mass effects, the addition of pegvisomant is the recommended option in the most recent guidelines for the management of acromegaly [1].

CAB in conjunction with pegvisomant

Two recent, small studies evaluated the addition of CAB to the treatment regimen of patients whose conditions remained uncontrolled under PEG therapy [34, 35]. In a prospective clinical trial involving 24 patients, CAB in monotherapy was up-titrated to a dose of 0.5 mg/day without observing significant changes in IGF-I [34]. With the addition of PEG 10 mg/day, normalization of IGF-I levels was observed in 68 % of the patients. When CAB was withdrawn, only 26 % of the patients remained with normal IGF-I levels. The combination therapy was only maintained for 12 weeks [34].

In a retrospective observational study, CAB was added to PEG treatment in 14 patients who were resistant to SSA [35]. Normalization of IGF-I levels was observed in 28 % of these patients. The average change in IGF-I levels was -18 ± 27 % [35]. Therefore, the use of CAB in conjunction with PEG can be an alternative treatment for acromegaly; however, additional studies are necessary because more data are available regarding the joint use of PEG and SSA compared to the CAB-pegvisomant combination, as reported in the previous section.

Side effects

The safety profile of CAB in acromegalic patients has not been evaluated in randomized-controlled trials or in studies involving large numbers of patients. Although the majority of side effects seem to be mild, there are concerns regarding some adverse events that were not previously evaluated in acromegalic patients—for example, increased awareness of CAB's association with impulse control disorders in patients with Parkinson's disease, restless leg syndrome and multiple system atrophy [36]. Recently, it

has been described in pituitary adenomas (mainly prolactinomas), with one study showing that impulse control disorders are 9.9 times more common in male patients taking DA than in the control group patients [37]. There are no studies evaluating impulse control disorders in acromegalic patients being administered CAB.

Valvar regurgitation induced by DA: is there a risk in acromegaly?

DAs were used for the treatment of Parkinson's disease until they were reported to increase the risk for severe valvar regurgitation [38, 39]. This was reported in patients using elevated doses of CAB that were as high as 3.5 mg/day [39]. This medication was discontinued for the treatment of Parkinson's disease; however, because the dose used in the treatment of pituitary adenomas is much lower, the drug continued to be used in this setting. Subsequently, there were several studies addressing the risk of valvar damage in prolactinoma and acromegaly patients, without clear evidence of clinically significant valvar disease [12, 40–42]. The majority of the studies evaluated patients treated for hyperprolactinemia, and the follow-up times were short to assure that CAB was not associated with a risk for valvar disease in the doses used in acromegaly treatment [40, 41, 43, 44]. In addition, acromegaly itself is associated with valvar disease [45–47], and there are some anecdotal reports of valvar damage associated with CAB therapy in acromegaly [48]. Therefore, close follow up with annual echocardiography is recommended in these patients if CAB is chosen as a therapeutic option.

Conclusions

CAB is an oral drug with a relative low cost in comparison to other drugs and has been used in the treatment of acromegaly; however, there is a paucity of evidence in the literature regarding its efficacy both in terms of biochemical and tumor volume outcomes, as well as with respect to its safety profile, especially with regard to its potential cardiac valvar side effects. Therefore, the lack of randomized-controlled clinical trials, the absence of studies with larger numbers of patients and the availability of other therapeutic options with better efficacy, and safety profiles are the main disadvantages to using CAB in the treatment of acromegaly. CAB remains a viable therapy only for patients with minimally active disease, and SSA use is supported by higher quality evidence than DA use.

Conflict of interest The authors have nothing to disclose.

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