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New Medical Approaches in Pituitary Adenomas

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Key Words

Growth hormone · Acromegaly · Prolactin · Prolactinomas · Adrenocorticotropic hormone · Cushing's disease · Clinically non-functioning adenomas

Abstract

Recently, the medical approach to patients with secreting and clinically non-functioning pituitary adenomas has received great impulse thanks to the availability of new, selective and long-lasting compounds with dopaminergic activity, such as cabergoline, and of somatostatin analogues provided in slow-release formulations, such as lanreotide and octreotide long acting release (LAR). In particular, the use of cabergoline has induced control of hyperprolactinaemia and tumour shrinkage in the great majority of patients with micro- and macroprolactinomas. Cabergoline treatment restores fertility both in women and men, and partially improves osteoporosis, one of the major complications of hyperprolactinaemia. In acromegaly, disease control (growth hormone [GH] <2.5–1.0 μg/l as a fasting or glucose-suppressed value, respectively, together with age-normalised insulin-like growth factor [IGF]-I) is achievable in more than half of patients receiving treatment with lanreotide or octreotide-LAR. Improvement in cardiomyopathy, sleep apnoea and arthropathy has been reported during GH/IGF-I suppression after pharmacotherapy. A synthetic GH analogue, B2036-PEG, that antagonises endogenous GH binding to its receptor-binding sites and a GH-releasing hormone antagonist that blocks the effect of this releasing factor on the hypothalamus and pituitary are presently under investigation in acromegaly. Preliminary studies have clearly demonstrated the effectiveness of the GH receptor antagonist in suppressing IGF-I levels in acromegalic patients previously unresponsive to somatostatin analogues. Beneficial effects of subcutaneous octreotide and lanreotide have also been reported in adenomas secreting thyroid-stimulating hormone, while the results of treatment with dopamine agonists or somatostatin analogues remain disappointing in patients with clinically non-functioning adenomas. In these patients the possibility of visualising in vivo the expression of D_2 receptors using specific radiotracers such as ^{123}I-methoxybenzamide has allowed selection of patients likely to respond to cabergoline. Scant effects of pharmacotherapy have also been reported in patients with adenomas secreting adrenocorticotropic hormone. However, some preliminary data suggest a potential use of cabergoline in combination with ketoconazole, or alone, in selected cases of Cushing's disease or Nelson's syndrome.

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Introduction

In recent years the medical approach to pituitary adenomas has greatly improved thanks to the availability of new, selective and long-lasting compounds with dopaminergic activity, such as cabergoline, and somatostatin analogues provided in slow-release formulations, such as lanreotide and octreotide long-acting release (LAR). In patients with acromegaly due to a growth hormone (GH)-secreting tumour or to ectopic GH-releasing hormone (GHRH) hypersecretion, promising new therapeutic agents have recently emerged in the form of competitive GHRH and GH antagonists which have been shown to effectively suppress GH and insulin-like growth factor (IGF)-I levels. Using these new compounds, the medical approach to pituitary adenomas has offered a high cure rate mostly in patients with prolactinomas and acromegaly, but a notable effect has also been reported in patients with thyroid-stimulating hormone (TSH)-secreting adenomas. However, results in patients with clinically nonfunctioning adenomas and Cushing's disease have been rather disappointing. This review summarizes the most recent studies on the effects of cabergoline, lanreotide and octreotide-LAR in patients with pituitary adenomas.

Prolactin-Secreting Pituitary Adenomas

Hyperprolactinaemia is a common finding in clinical endocrine practice, causing infertility, gonadal and sexual dysfunction in both sexes [1]. It may have differing aetiology but, once drugs are excluded, microadenomas (<10 mm) or macroadenomas (>10 mm) are the most common cause [1]. Macroadenomas occur less frequently than microadenomas, and more frequently in men than in women. This is probably due to disease duration and the gradual development of symptoms; however, natural history studies suggest that the majority of microadenomas (over 90%) remain small over time and only a small proportion grow to become macroadenomas [2]. It has therefore been hypothesised that macroadenomas may be biologically different from microadenomas.

The objectives of treatment of hyperprolactinaemia are to normalise prolactin (PRL) levels thus resolving its clinical consequences (infertility, sexual dysfunction and osteoporosis), to remove the tumour mass thus relieving visual and cranial nerve function disturbance, to preserve residual pituitary function and, if possible, to prevent disease recurrence or progression. In the past, before medical therapy for hyperprolactinaemia became available, therapy consisted of surgical resection and/or pituitary irradiation [3, 4].

The management of prolactinomas may involve medical therapy using dopamine agonists with selective activity on D_2 receptors, radiotherapy or surgery, usually transsphenoidal. Treatment may utilize one or all of these methods and differs according to whether a micro- or a macroprolactinoma is involved.

Microprolactinomas

In microprolactinomas, transsphenoidal surgical resection normalises PRL levels, restores normal menses and stops galactorrhoea in more than 80% of patients [3, 4]. Success rates are reported to be higher in patients with basal PRL levels below 200 μg/l and amenorrhoea for less than 5 years [3]. However, PRL normalisation after surgery is variable, ranging from 35 to 70% in different series [5–10]. The risks of complications and hypopituitarism are small. Recurrence rates vary considerably between different series and may affect up to 50% of those initially cured by surgery [3, 4, 10]. In another series the long-term cure rate was as high as 74%, with an initial cure in 90% and a recurrence rate of 16% [4].

However, at present the majority of patients with microprolactinomas are treated by pharmacotherapy. For over 20 years bromocriptine has been the standard drug for hyperprolactinaemia since it not only inhibits PRL synthesis and secretion but also reduces cellular DNA synthesis and tumour growth [11]. In more than 80% of patients, suppression of PRL levels and tumour shrinkage are obtained after therapy with bromocriptine at doses of 2.5–5.0 mg/day [11]. In 5–10% of patients, the appearance of side effects (nausea, dizziness and postural hypotension) is a limiting factor in continuing treatment [3, 4, 11]. The development of psychoses during dopamine agonist therapy has been reported in rare cases [12]. In a minority of patients, complete or partial resistance to bromocriptine treatment is observed (see below).

Recently, two selective D_2 agonist compounds, quinagolide and cabergoline, became available for the treatment of hyperprolactinaemia in a number of European countries. Both compounds have the advantage of being administered at doses lower than that of bromocriptine thus causing fewer side effects. Quinagolide has been shown to be effective in most patients [13, 14] and is better than bromocriptine in patients with tolerance-related problems [15, 16]. In a multicentre comparative study, cabergoline treatment induced stable normoprolactinaemia in 83% of patients compared with 59% of those treated with bromocriptine [17]. Ovulatory cycles or preg-

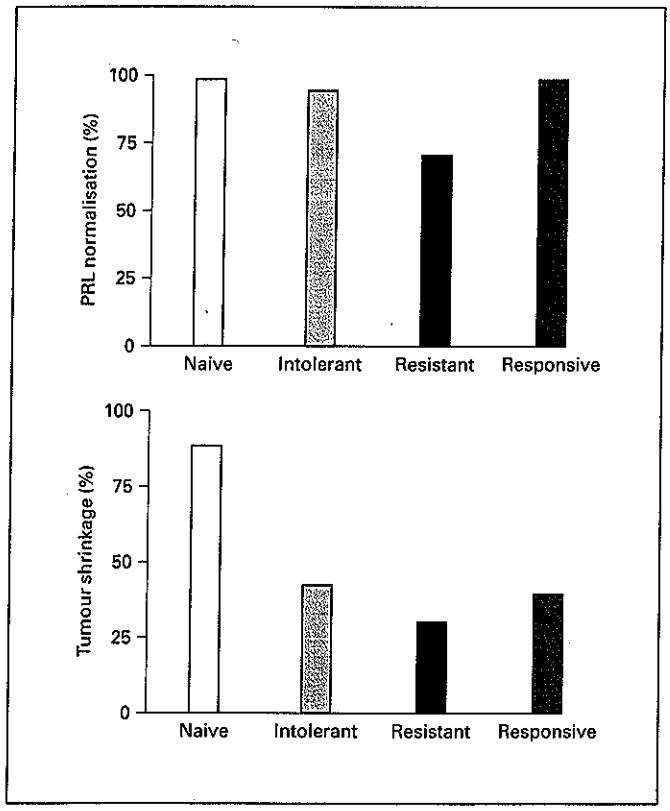

Fig. 1. Prevalence of PRL normalisation (<25 and <15 μg/l, in men and women, respectively) and tumour shrinkage (>80% reduction compared with basal volume) in patients with macroprolactinomas.

nancies were recorded in 72% of women treated with cabergoline and in 52% of those treated with bromocriptine [17]. Furthermore, cabergoline induced significantly less frequent, less severe and shorter lived side effects (particularly nausea and vomiting) compared with bromocriptine [17]. In a very recent retrospective study of 455 patient files [18], cabergoline treatment normalised serum PRL levels in 86% of patients: in 92% of 244 patients with idiopathic hyperprolactinaemia or microprolactinoma, and in 77% of 181 patients with macroprolactinoma. Side effects were noted in 13% of patients, but only 3.9% discontinued therapy as a result [18]. The median dose of cabergoline at the start of therapy was 1.0 mg/week but could be reduced to 0.5 mg/week once control was achieved. In patients with macroprolactinoma a higher median cabergoline dose (1.0 mg/week) was needed than in those with idiopathic hyperprolactinaemia or microprolactinoma (0.5 mg/week) [18].

Macroprolactinomas

In macroprolactinomas, transsphenoidal surgery is less successful. In a study by Molitch et al. [4], 32% of patients appeared to be cured initially, with a 19% recurrence rate and a long-term cure rate of only 26%. Notable tumour shrinkage is, however, achievable in most cases after short-term treatment with dopamine agonists, particularly with cabergoline [18–22] and quinagolide [13–16]. As for other pituitary tumours, radiotherapy is applied in large invasive macroprolactinomas when medical treatment fails to suppress PRL levels and/or induce tumour shrinkage. Radiobiological damage rarely occurs if a linear accelerator is used, therapy is delivered through three fields and a fractionated dose of less than 200 rad/day is delivered at a total dose of 4,500 rad [23, 24].

Thanks to the high success rate of dopamine agonists, however, radiotherapy is rarely applied to prolactinomas, while pharmacotherapy is widely considered the first treatment option in macroprolactinomas. Cabergoline treatment at weekly low doses for 12–24 months induced marked tumour shrinkage with complete disappearance of tumour mass in 26.1–36.4% of cases [18–22]. In our preliminary experience with cabergoline, a tumour volume reduction of >80% on magnetic resonance imaging (MRI) occurred in 14 of 23 patients (61%) and a 41.8 ± 3.4% volume reduction was already evident after 3 months [21]. Complete tumour disappearance on MRI occurred after 6 months of treatment with cabergoline in 1 patient, and in 5 patients after 1 year of treatment [21].

The majority of studies on macroprolactinomas include patients who had never been treated with other dopamine agonists or who were treated with bromocriptine for brief periods of time because of intolerance. In a multicentre study, cabergoline treatment induced tumour shrinkage in 60% of patients previously treated with other dopamine agonists and in 82.3% of untreated patients [20]. In another recent multicentre study of 181 patients with macroprolactinomas, cabergoline treatment induced tumour shrinkage in 67% of cases and improvement of visual field defects in 70% of patients [18]. In a recent review of our cases which included 110 patients with macroprolactinoma, notable tumour mass shrinkage was observed in the majority (88.5%) of patients [25]. Tumour mass disappeared in 57.7% of 26 naive patients. Tumour shrinkage and/or disappearance were also observed in patients previously treated with bromocriptine or quinagolide, but to a lesser degree (fig. 1). Interestingly, in naive patients the tumour-shrinking effect of cabergoline was very rapid, occurring even after the first administration of 0.5 mg of the drug [25].

Infertility and osteoporosis are the two main clinical consequences of hyperprolactinaemia. The beneficial effect of treatment on the recovery of fertility in hyperprolactinaemic women has been widely reported, while data on the recovery of fertility in men are extremely limited. In a preliminary study in men with prolactinoma [26], cabergoline treatment at a dose of 1–2 mg/week rapidly induced the restoration of sperm quality, significantly increasing the number of sperm even after 1 month of treatment, which was earlier than with bromocriptine treatment.

As far as osteoporosis is concerned, in women the recovery of hypogonadism, more than the suppression of PRL levels, was associated with an improvement in bone mass [27, 28]. In men, data concerning the recovery of bone loss are scant. Treatment with bromocriptine, quinagolide and/or cabergoline for 18 months induced a significant increase in bone mineral density in hyperprolactinaemic males [29], but did not significantly modify the T score, indicating that a longer period of treatment could be necessary to achieve this. In addition, the age of onset of hyperprolactinaemia also plays a relevant role in the potential reversibility of osteopenia: in young/adolescent patients with prolactinoma, 2 years of treatment with bromocriptine, quinagolide and/or cabergoline, though normalising PRL levels in the large majority of patients, did not significantly modify bone mass (fig. 2) [30].

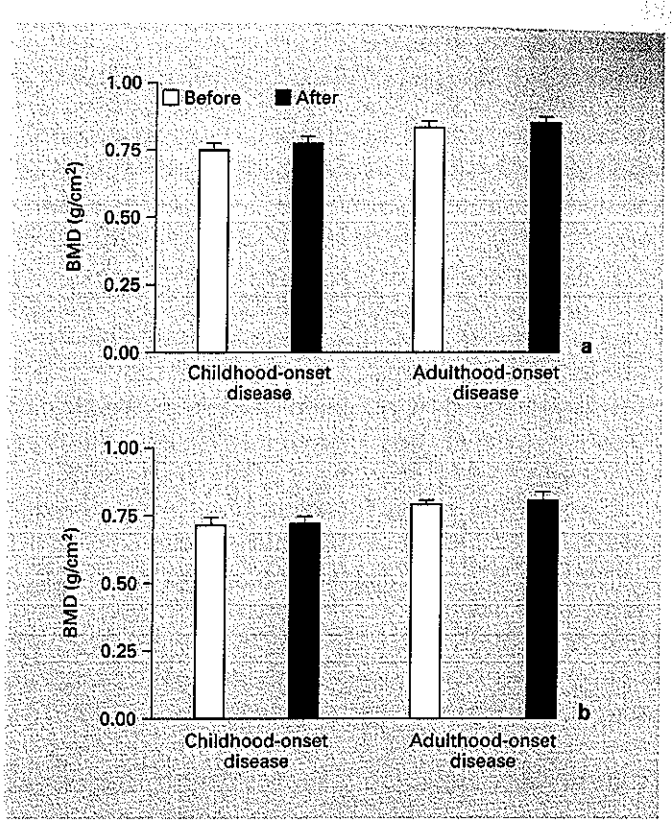

Fig. 2. Bone mineral density (BMD) in the lumbar spine (**a**) and femoral neck (**b**) in patients with hyperprolactinaemia before and 24 months after treatment with bromocriptine, quinagolide and/or cabergoline. Patients are divided according to age of onset of hyperprolactinaemia: childhood vs. adulthood onset.

Resistance to Dopamine Agonists

The definition of therapy resistance to dopamine agonists is controversial. One definition is the absence of serum PRL level normalisation and/or tumour shrinkage after at least 3 months of treatment with bromocriptine at a dose of 15 mg, or quinagolide at a dose of 0.6 mg [31–33]. These doses are rather high for the treatment of hyperprolactinaemia. Another definition is a <50% reduction in serum PRL levels despite increasing the daily dose to at least 15 mg [34]. However, true resistance can only be documented by molecular biology studies, demonstrating the absence or poor expression of D_2 receptors on the membrane surface of the tumour cells [35, 36] or abnormalities at the postreceptor level [35, 36]. Another possibility was recently suggested by several studies which demonstrated the presence of a positive correlation between the response to quinagolide (in terms of PRL normalisation and tumour shrinkage) and the uptake of ^{123}I-methoxybenzamide (^{123}I-IBZM), a specific radiotracer for D_2 receptors, in pituitary tumours [37–39]. This approach, although needing to be confirmed in larger series, seems to offer the possibility of studing the receptor profile in vivo so as to predict the clinical response to D_2 agonists. However, in the majority of patients, a partial, rather than a complete, therapy resistance occurs and thus an increase in the dose of the drug could achieve normoprolactinaemia.

The effectiveness of any treatment is strictly related to tolerability and patient compliance. In a previous study we demonstrated that tolerability and compliance were better during cabergoline than during quinagolide or bromocriptine treatment [40]. Cabergoline treatment normalised PRL levels in 15 of 19 patients with macroprolactinomas and in all 8 patients with microprolactinomas. Treatment with quinagolide has also been demonstrated to be more effective than bromocriptine in several poorly responding patients [14, 16]. Not all patients responded satisfactorily to cabergoline and quinagolide although the response to cabergoline was better in some cases [32, 33, 40, 41]. One explanation was that cabergoline binds the

receptor significantly longer than quinagolide [42] and induces less severe and shorter lasting side effects [43].

In conclusion, pharmacotherapy with dopamine agonists remains the most appropriate first-line treatment for macroprolactinoma with the exception of poorly responding or resistant patients. Dopamine agonists induce tumour shrinkage and quite often also cause tumour disappearance. Consequently, visual field defects rapidly improve in the majority of patients often without requiring surgical tumour debulking. However, theoretically in these patients pharmacotherapy must be continued indefinitely [44]. The dose can be reduced over time, and in 10–20% of patients drug discontinuation does not cause recurrence of hyperprolactinaemia [45]. In particular, we have recently observed the persistence of normoprolactinaemia in 8 of 23 patients with microprolactinomas after 2–4 months of cabergoline withdrawal and in 4 of them normoprolactinaemia was still present 12 months after withdrawal [46]. In microprolactinomas the treatment strategy could be reconsidered on the basis of the high cure rate of transsphenoidal adenomectomy [47]. Surgery is also recommended in patients who are severely intolerant to dopamine agonists.

GH-Secreting Pituitary Adenomas

GH-secreting adenomas are the most frequent cause of acromegaly, but are relatively rare with a prevalence of 50–80 cases/million and an incidence of 3–4 new cases/million per year, an equal frequency in both sexes, and an age prevalence of between 55 and 70 years [48, 49].

Treatment of acromegaly has different objectives: (1) tumour removal with resolution of its mass effects; (2) restoration of normal basal and stimulated GH secretion; (3) relief of symptoms directly caused by GH excess; (4) prevention of progressive disfigurement, bone expansion, osteoarthritis and cardiomyopathy, which are disabling long-term consequences, as well as prevention of hypertension, insulin resistance, diabetes mellitus and lipid abnormalities, which are risk factors for vascular damage, and (5) possibly reversing the poor long-term outcome. However, to date it is still unclear what level of GH suppression is needed to achieve treatment success; the disease is currently considered to be under control when fasting GH levels are <2.5 μg/l, glucose-load-suppressed GH levels are <1 μg/l and IGF-I levels are normalised for age [50].

The currently available treatment options for acromegaly include surgery, irradiation and pharmacological suppression of GH levels by means of dopamine agonists or somatostatin analogues, either alone or in combination. Surgical removal of the pituitary adenoma remains the first therapeutic option in most cases [48, 50, 51], although primary pharmacotherapy has recently been proposed [52]. Irradiation or pharmacological suppression of GH excess can be used following unsuccessful surgery or as individualized primary therapy in elderly patients [51].

Dopamine agonists are less effective in GH-secreting adenomas than in PRL-secreting adenomas and are shown to be primarily effective in GH-secreting tumours that co-secrete PRL or that exhibit immunostaining for PRL [53, 54]. In a collection of 28 series including over 500 patients with acromegaly, bromocriptine lowered GH levels to <10 μg/l in 50% of cases, but to <5 μg/l in only 10–20% of cases [55]. It also produced a symptomatic improvement in up to 70% of patients, but tumour shrinkage occurred in only 10–15% [50]. Side effects such as nausea, vomiting, postural hypotension, nasal congestion and depression appearing after administration of the first dose can be prevented in most patients by starting at lower doses. However, as high doses are needed for therapeutic efficacy, side effects are often a limiting factor. We first reported that cabergoline was effective only in 1 of 11 patients treated at a cabergoline dose of 2 mg/week [54]. In contrast, Abs et al. [56], in a multicentre study, observed that cabergoline at a maximal weekly dose of 3.5 mg induced normalisation of IGF-I levels in 39% of cases and significantly reduced IGF-I levels in a further 28%. However, when the prevalence of IGF-I normalisation was evaluated in patients with mild disease, diagnosed on the basis of a basal IGF-I concentration below 750 μg/l, it rose to 53% [56]. Tumour shrinkage was demonstrated in 13 of 21 patients and a tumour reduction of 50% in 5 GH/PRL-secreting adenomas. Cabergoline was well tolerated by all patients and only 2 patients withdrew from treatment on the grounds of nausea [56]. In another study, cabergoline was administered to 18 acromegalic patients; 10 had previously been shown to be sensitive to dopamine and 8 had been shown to be resistant to somatostatin analogues [57]. Serum GH levels were decreased from a median value of 6.6 to 3.5 μg/l, while IGF-I values were decreased from a median value of 720 to 375 μg/l [57]. Individual GH levels decreased <2 μg/l in 5 patients, and between 2 and 5 μg/l in a further 5 patients, while IGF-I levels were suppressed to <50% of baseline in 8 patients and normal age-adjusted IGF-I values were achieved in 5 patients (27%) [57]. In comparison with the efficacy of bromocriptine in the 10 suitable patients, a greater effec-

tiveness of cabergoline was shown as IGF-I levels decreased by 46.8% on cabergoline treatment, and by 31% on bromocriptine treatment [57]. Adenoma shrinkage was documented in the 3 patients whose pituitary imaging was repeated during cabergoline [57]. In another study using increasing doses of cabergoline up to 3.5 mg/week, 7 of 10 patients with active acromegaly showed a fall in GH to 33% and in IGF-I to 67% of basal values, but only 2 achieved biochemical remission [58]. Four of the ten patients were unable to tolerate the maximum dose of 1 mg daily [58].

However, somatostatin analogues have been widely shown to be more effective than dopamine agonists in acromegaly. Octreotide, a long-acting synthetic somatostatin analogue with a half-life of 80–100 min, was first used to treat acromegaly in the mid-1980s [59]. Many subsequent studies indicated that octreotide reduced GH in over 90% of patients, suppressing GH levels to <5 μg/l in half of them [48–50, 60]. A combined analysis of 557 patients treated worldwide showed that octreotide administration normalised IGF-I levels in 48.5% and shrank tumour size (<20% of baseline size) in 40.3% of patients [50]. This latter effect seems to favour the complete removal of macroadenomas at surgery, and reduce intraoperative manipulation of adjacent structures [48]. To this extent, we have proposed that a short, presurgical treatment with octreotide could improve the clinical status of acromegalic patients and reduce postoperative complications [61]. Soon after the first doses of subcutaneous octreotide, lanreotide or octreotide-LAR, clinical signs and symptoms, in particular headache, hyperhidrosis and joint pain, are significantly reduced [48–52, 60, 62–64]. Lanreotide was effective in patients previously responsive to subcutaneous octreotide, but was better tolerated thus improving patient compliance [62–64]. Treatment with lanreotide for 3 years produced GH and IGF-I normalisation in 14 of 22 patients but nine patients had to increase the injection frequency to 1 every 10 days for optimal control [65]. Loose stools, nausea and/or abdominal pain were reported by half of the patients for the first 2 days following injection and approximately 20% of patients developed new gallstones [62–65]. In a recent survey of 118 patients with acromegaly treated for 24 months with lanreotide, 25 of whom were newly diagnosed, we demonstrated that after 6, 12 and 24 months of therapy, disease control was achieved in 63–77% of patients (fig. 3) [66]. Reduction in tumour size was documented in 5 of 23 naive patients (22%) and in 5 (5.9%) of 84 octreotide-pretreated patients with evident tumour remnants [66]. Lanreotide treatment was well tolerated by all patients

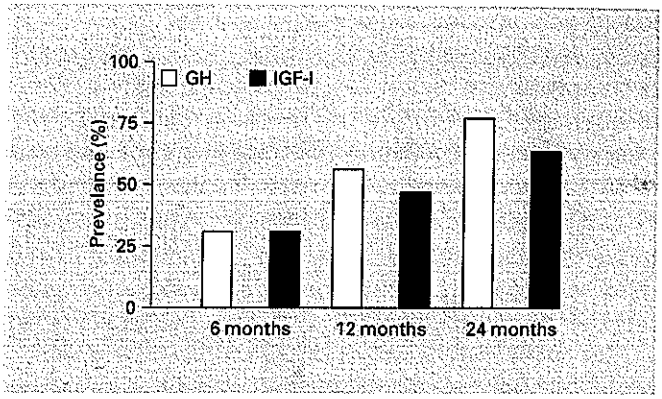

Fig. 3. GH (<2.5 μg/l) and IGF-I (age-adjusted) normalisation in 118 patients with acromegaly treated for 6–24 months with slow-release lanreotide [65].

only 2 (1.7%) withdrawing from treatment due to severe side effects [66].

Octreotide treatment improves obstructive and central sleep apnoea, as demonstrated by the reduction in the number of apnoeic episodes and in the degree of blood oxygen desaturation [67].

Octreotide and lanreotide have also been shown to decrease left ventricular mass [68–72] and to improve diastolic function [68–72]. An improvement in systolic function was demonstrated in patients with overt heart failure [73] and in patients without symptoms of cardiac disease after 1 year of treatment with octreotide if they achieved disease control [74]. Arthropathy, which is one of the major causes of morbidity with the disease [50, 67], was significantly improved by octreotide and lanreotide treatment as demonstrated by a significant decrease in shoulder, wrist and knee joint thickness [75, 76].

Acromegalic patients were also found to have an age-independent increase in prostate volume [77] that was significantly reduced after octreotide treatment [78].

The increased incidence of gallbladder abnormalities (sediment, sludge, microlithiasis and gallstones) seems to be associated with low morbidity, and can be managed conservatively as in other patients with asymptomatic cholelithiasis [50].

Using octreotide-LAR, reductions in GH levels to <5 μg/l were recorded in 86–100% of patients, to <2 μg/l in 39–75% of patients and to <1 μg/l in 24–40% of patients [79–81], without any evidence of tachyphylaxis after up to 34 months of therapy [79–81]. Tumour shrinkage was also reported [79–81]. As with the other formulations, octreotide-LAR was well tolerated and the mild-to-

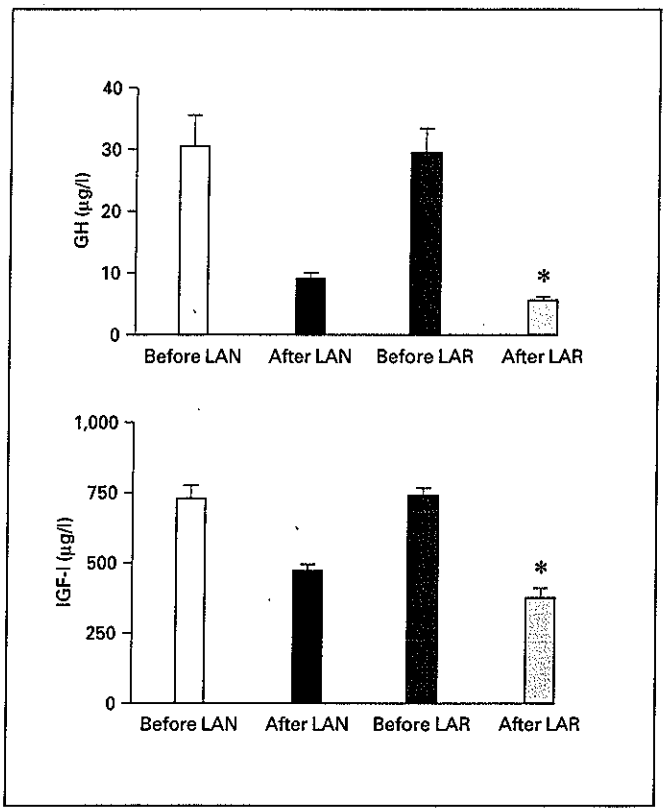

Fig. 4. Serum GH and IGF-I levels before and after treatment with slow-release lanreotide (LAN) and octreotide-LAR (LAR) in 30 patients selected on the basis of poor response to lanreotide treatment. *$p < 0.005$.

moderate side effects experienced by up to 50% of the patients were of short duration and often subsided with continued drug administration [79–81]. The incidence of gallbladder abnormalities was higher in patients who had previously undergone long-term treatment with subcutaneous octreotide [79]. In a selected group of 30 patients who did not achieve disease control after long-term treatment with lanreotide, GH and IGF-I levels were lower after octreotide-LAR than after lanreotide (fig. 4): GH concentrations of ≤ 2.5 µg/l were achieved in 11 patients taking octreotide-LAR, and IGF-I normalisation was observed in 15 patients.

Recently, a novel potential option has appeared for the medical treatment of acromegaly. A synthetic GH analogue, B2036-PEG, that antagonizes endogenous GH binding to its receptor-binding sites and a GHRH antagonist that blocks the effect of this releasing factor on the hypothalamus and pituitary are under investigation [82, 83]. Preliminary studies have clearly demonstrated the effectiveness of the GH-receptor antagonist in suppressing IGF-I levels. Acromegalic patients previously unresponsive to somatostatin analogues achieved normal IGF-I levels after daily subcutaneous treatment with B2036-PEG [84, 85]. Only mild side effects and no significant antibody formation have been observed in the first randomised, double-blind trials [85].

In conclusion, it is still not known whether the poor perspectives of acromegalic patients in terms of mortality from cardiorespiratory or neoplastic diseases can be reversed by any treatment. One preliminary study suggests that normal survival is attained in acromegalics with post-treatment GH levels of <2.5 µg/l, but not in those with higher levels [86]. Moreover, at least five different somatostatin receptor subtypes exist and are expressed in normal and neoplastic somatotrophs [60], whereas both octreotide and lanreotide act predominantly on type-2 and type-5 receptors; therefore there is a possibility that these are not the best analogues for treating acromegaly. Since a small but appreciable proportion (about 15–20%) of acromegalic patients do not respond well to somatostatin analogues, indicating that the receptor subtypes can be abnormally expressed or regulated, future research should produce selective analogues able to bind the other somatostatin receptor subtypes. Somatotroph-specific cytotoxic agents, targeted by agonists or antibodies to the GHRH receptor, to selectively eliminate residual tumour cells, and GH-receptor antagonists to block the peripheral effects of GH will increase the therapeutic possibilities in acromegaly.

TSH-Secreting Pituitary Adenomas

This adenoma histotype is rare. Frequently these are macroadenomas at diagnosis presenting with mass effect symptoms such as headache and visual disturbances, together with variable symptoms and signs of hyperthyroidism [87, 88]. Transsphenoidal surgery is the first treatment approach to these tumours. However, since the majority of these adenomas are macroadenomas, which tend to be locally invasive, surgery alone fails to normalise TSH and thyroid hormone levels in over 50% of cases. In adults, radiotherapy is recommended as routine adjunctive therapy when surgery has not been curative [87].

There is very little success with dopamine agonists for treatment of these tumours [87, 89]. In contrast, since TSH-secreting adenomas express somatostatin receptors [90], biochemical disease can be controlled with octreotide therapy in most patients; TSH levels have been

reported to normalise in 79% of patients and tumour shrinkage can occur in 50% of cases [87–93]. Octreotide treatment is also considered useful preoperatively as it facilitates tumour removal [87]. The dose of octreotide in patients with TSH-secreting adenomas to achieve TSH normalisation is reported to be lower than that needed to suppress GH in GH-secreting adenomas [87–93]. Lanreotide at a dose of 0.5 mg was demonstrated to inhibit acute TSH secretion in TSH-secreting adenomas similar to 0.15 mg of octreotide [94]. In chronic treatment, lanreotide reduced plasma TSH and normalised free thyroxine and free triiodothyronine levels, suggesting its use in the long-term medical treatment of these adenomas [94].

Clinically Non-Functioning Pituitary Adenomas

Clinically non-functioning pituitary adenomas (NFAs) represent a very heterogeneous group of tumours since a consistent proportion of them (>90%) are shown to secrete low amounts of intact follicle-stimulating hormone (FSH) and luteinising hormone (LH) and/or their α and β subunits either in vitro or in vivo [92, 95]. The first approach in these adenomas is transsphenoidal surgery to remove the tumour mass and decompress parasellar structures. As in the other adenoma histotypes, surgery has a low morbidity and improves visual loss in the majority of cases [96, 97]. Hypopituitarism is partially recovered after surgery in these patients [96–100]. Postoperative radiotherapy is applied in patients with subtotal tumour removal to prevent tumour regrowth and even reduce residual tumours [98–100], but is burdened by a high prevalence of panhypopituitarism [98–100].

Medical therapy has its rationale after surgery to delay radiotherapy and the potential occurrence of hypopituitarism. The introduction of dopamine agonists in the medical therapy of NFAs was based on the observation that dopamine receptors are present in vitro in NFA cells, as in prolactinoma cells [101–103]. Bromocriptine, the first dopamine agonist available for therapeutic purposes, was used in NFAs with disappointing results, probably due to the lower amount and affinity of D_2 receptors expressed on NFAs than on prolactinoma cells [89].

Only a few studies have reported on the efficacy of quinagolide in the treatment of these tumours [39, 104, 105]. Twelve patients were treated with quinagolide at a dose of 0.3–0.6 mg/day: 3 patients had an NFA, 8 an α-subunit-secreting adenoma and 1 an FSH/LH-secreting adenoma. Treatment for 3–12 months reduced gonadotropin and/or α-subunit levels in all patients [39, 104, 105]. A significant tumour shrinkage was documented; however, only in 4 of 12 patients.

No study has reported on the efficacy of cabergoline in NFAs. In preliminary experience [106], cabergoline was administered to 10 patients with NFAs who underwent scintigraphy with ^{123}I-IBZM prior to therapy. ^{123}I-IBZM was used to detect in vivo the presence of D_2 receptors on pituitary tumours [37–39, 103]. A significant correlation between tracer uptake in the pituitary adenoma and clinical response to quinagolide or bromocriptine treatment was observed in a few selected patients with PRL, GH or α-subunit-secreting adenomas [37–39, 103]. This approach might be of great clinical relevance in patients with NFAs, in whom the lack of biochemical markers makes monitoring the efficacy of pharmacotherapy very difficult. Among the 10 patients with NFAs, no uptake was detected in 6 and a moderate uptake was detected in 2; however, intense uptake was observed in the remaining 2 patients [106]. After 12 months of treatment with quinagolide or cabergoline, suppression of PRL levels was found in all 10 patients with NFAs, a significant reduction in α-subunit levels was obtained in 9 of 10 patients; in 4 of 8 patients α-subunit levels were normalised. A significant adenoma shrinkage was recorded only in the 2 of 10 patients with NFAs with intense pituitary uptake of ^{123}I-IBZM [106].

Similar to that observed in patients with TSH-secreting adenomas, treatment with somatostatin analogues, mostly with subcutaneous octreotide, was based on evidence that these tumours express somatostatin receptors [101–103]. Several clinical trials reported, however, that tumour reduction occurred in only 11–13% of cases, indicating a weak correlation between somatostatin receptor expression and treatment efficacy with octreotide in these patients [101–103, 107, 108]. Octreotide treatment was followed by a rapid improvement in headache and visual disturbances, without any change in tumour volume [108, 109]. This effect was likely due to the in vitro evidence that octreotide inhibits growth of new vessels and endothelial cells, leading to the hypothesis that the visual improvement was more likely to be due to a direct effect of octreotide on the retina and the optic nerve than to an effect mediated by the somatostatin receptors expressed on the pituitary tumour [103].

In conclusion, as patients with NFAs are difficult to monitor due to the lack of biochemical markers of overproduction, ^{123}I-IBZM scintigraphy can be proposed prior to the start of treatment with quinagolide or cabergoline. Intense ^{123}I-IBZM uptake in patients with NFAs might be predictive of a good response to chronic treat-

ment with quinagolide or cabergoline [106], and those patients who might benefit from treatment could be selected on the basis of tracer uptake. Immunostaining for D_2 receptors has recently been provided [110]. It should be investigated whether immunostaining for D_2 receptors would be a less expensive method of characterising tumoural receptor status in vitro on surgically removed tissues than the current in vivo methods.

ACTH-Secreting Pituitary Adenomas

Transsphenoidal adenomectomy is the treatment of choice for adenomas-secreting adrenocorticotropic hormone (ACTH). Surgical excision is successful in the majority of patients, with initial remission rates of 70–98% and long-term cure in 50–98% in most studies [10, 92].

Neuromodulatory drugs affect ACTH secretion mainly by acting at the hypothalamic level. Since ACTH secretion is sensitive to hypothalamic control even in the presence of an ACTH-secreting adenoma, compound agonists and antagonists on the hypothalamic-pituitary axis may influence ACTH secretion in Cushing's disease [111]. Bromocriptine, at doses ranging from 3.75 to 30 mg/day, was tested in patients with Cushing's disease, and produced controversial results. Acute bromocriptine administration decreased plasma ACTH levels in about half of the patients, but a decrease by more than 50% was reported in only 18% of patients [112]. Better therapeutic results have been reported using very high doses ranging from 17.5 to 40 mg daily [113]. Bromocriptine has also been shown to inhibit the proliferation of murine ACTH-secreting pituitary adenoma (AtT-20) cells [114]. The anti-tumoural activity of bromocriptine was inhibited both by actinomycin D and cycloheximide, suggesting that it was dependent on new RNA and protein synthesis; the results of DNA fragmentation assays and cell cycle analysis clearly demonstrated that bromocriptine induced apoptosis in AtT-20 cells [114].

No data are presently available for cabergoline or quinagolide. One patient with pituitary-dependent Cushing's disease who refused transsphenoidal surgery was treated with ketoconazole and cabergoline and had a total remission [115]. The patient became pregnant during treatment and delivered a healthy child [115].

In Nelson's syndrome, medical therapy could play a role since in vitro studies have demonstrated that dopamine agonists, cyproheptadine and sodium valproate inhibit the release of corticotropin-releasing hormone both directly and indirectly [111, 113]. A marked reduction in plasma ACTH, after a single oral dose or during chronic treatment with bromocriptine, was observed in some patients with Nelson's syndrome [116], although other studies have failed to demonstrate such an effect [117]. In 1 patient we reported that treatment with cabergoline for 1 year at a dose of 2 mg/day was able to induce a complete clinical and biochemical remission of Nelson's syndrome [118]. Cabergoline induced the disappearance of the pituitary adenoma as documented by serial MRI. Withdrawal from cabergoline was rapidly followed by an increase in ACTH levels, necessitating renewed treatment [118].

In conclusion, data on the potential use of cabergoline in Cushing's disease and Nelson's syndrome are lacking. However, knowledge of the pathophysiology of ACTH secretion supports a role for dopamine agonists in the pharmacotherapy of these disorders. Further data are needed to clarify this issue.

Conclusions

The medical approach to pituitary adenomas has improved in recent years due to the availability of effective, well-tolerated and safe compounds able to suppress tumoural endocrine hypersecretion and, in some instances, to reduce tumour mass. Other promising alternatives are under investigation, such as GH and GHRH antagonists, which should enable satisfactory control even in difficult cases of acromegaly. Use of these new compounds will open up new pathways in the medical management of patients with pituitary adenomas, possibly making surgical removal of the tumour an option for patients intolerant or resistant to pharmacotherapy, as is currently the case with prolactinomas.

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