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Pharmacological Therapy for Acromegaly

A Critical Review

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Abstract

The treatment of acromegaly has changed considerably over the last few decades. In the late 1970s, the introduction of the dopamine receptor agonists made it possible to reduce growth hormone (GH) secretion by somatotropinomas for the first time. Thereafter, the introduction of the somatostatin analogues in the early 1980s had major implications. Recently, the first data on the use of genetically engineered human GH receptor (GHR) antagonists that block GH actions have become available. These GHR antagonists reduce both the biochemical abnormalities of acromegaly, as well as improve clinical signs and symptomatology.

In this article we firstly review available data on dopamine agonists. Currently these compounds should be considered in patients with a mixed GH-prolactin secreting pituitary adenoma and/or those in whom pre-treatment insulin-like growth factor (IGF)-I concentrations are below 750 μg/L. We then discuss the somatostatin analogues. These compounds are capable of achieving biochemical control of GH and IGF-I in 50–60% of patients and tumour shrinkage in some 30%. In particular, candidates for treatment with these compounds are those patients who have undergone an unsuccessful transsphenoidal operation or who await the therapeutic effect of external pituitary irradiation. In selected patients primary medical therapy with somatostatin analogues is certainly a feasible option. To date, pegvisomant is the only available member of a new class of drugs that was especially designed to block the GHR. Pegvisomant is the most effective treatment for normalising IGF-I concentrations and appears to have a good safety profile. However, liver function tests should be regularly monitored and tumour size should be closely followed. Finally, we propose a treatment algorithm for acromegaly.

1. Acromegaly

1.1 Causes of Acromegaly

In virtually all patients with acromegaly the cause is a benign growth hormone (GH)-secreting pituitary adenoma. The role of the pituitary gland as being responsible for 'the hormone that accelerates skeletal growth' or the 'hormone of growth' was first acknowledged by Harvey Cushing.[1,2] Acromegaly is a rare disease due to prolonged hypersecretion of GH. In 1909 Cushing reported that the clinical symptoms of acromegaly remitted after partial hypophysectomy, thus pointing to the pituitary as playing a central role in the cause of acromegaly.[3,4] He also recognised the general role that the pituitary gland has in the regulation of the endocrine system and postulated that certain diseases could be explained by pituitary hypo- or hyperfunction.[1]

Somatotroph adenomas can be part of syndromes such as the McCune-Albright syndrome, multiple endocrine neoplasia I and, occasionally, as isolated familial tumours.[5-9] In extremely rare cases, acromegaly can be caused by ectopic GH-releasing hormone production.[10,11]

1.2 Aims of Therapy

Patients with untreated acromegaly have approximately twice the mortality rate of healthy individuals matched for age; this is generally attributable to cardiovascular disorders and cancer.[12-14] As a result, all patients with acromegaly, even those who are asymptomatic, should be treated. Acromegaly can also lead to disfigurement. Finally, the sellar

mass can lead to substantial complications such as visual field defects, blindness and headaches.[5] Thus, the aims of therapy are to revert the life expectancy to that of the general population, to correct clinical symptoms and signs, and to prevent or revert sellar mass effects. At the same time care should be taken to preserve anterior pituitary function.

1.3 Available Treatment Modalities

Currently available treatment modalities consist of surgery, radiotherapy and medication. Unfortunately, surgery cures only 60% of patients and less than half of patients with macroadenomas (which constitute the majority of patients with acromegaly).[14,15] The effect of radiotherapy is delayed and variable with a high incidence of late panhypopituitarism.[16-23] Available medical treatment modalities are dopamine agonists, somatostatin analogues and GH receptor (GHR) antagonists. Dopamine agonists have limited efficacy and tolerability and are, in general, less effective than the somatostatin analogues.[24,25] Long-acting somatostatin analogues are given every 2–4 weeks and normalise serum insulin-like growth factor-I (IGF-I) levels in about 65% of patients.[26-29] This still leaves at least one-third of patients eligible for a more effective medical therapy. Very recently, a new class of drugs has been specially designed to block the GHR and, therefore, GH action. To date, pegvisomant is the only available member of this new class of drugs.

1.4 Criteria for Cure

Generally speaking, cure can be defined as the situation in which serum GH and IGF-I are returned to normal. GH pulsatility should also be normal and GH should be suppressed after an oral glucose load. In order to be able to compare treatment results strict biochemical criteria for cure have been defined in recent years.[30] According to these criteria, cure is defined as circulating IGF-I levels that are reduced to an age-adjusted normal range and nadir GH after an oral glucose load <1 μg/L.[30] However, relevant data have shown that a GH level <2.5 μg/L (measured with a polyclonal radioimmunoassay) is associated with a reduction of mortality in patients with acromegaly.[31,32] Unfortunately, GH levels <2.5 μg/L are not always associated with normal IGF-I levels.[33] Because normalisation of IGF-I is associated with a reduction in the excess mortality of acromegaly this criterion is an essential part of the definition of cure.[14,30,31] In this respect it is important to note that that the assays used for the diagnosis, management and follow up of acromegaly, that is, GH and (total) IGF-I must have adequate sensitivity (for GH, at least 0.5 μg/L), established validity, specificity and reliability as well as uniform reproducibility.[34,35]

Regardless of these biochemical criteria it is important to ablate or reduce tumour mass and prevent its recurrence, and alleviate significant co-morbid features, especially cardiovascular, pulmonary and metabolic derangements.[30,36,37]

2. Dopamine Agonists

2.1 Introduction

Dopamine is a small and relatively simple molecule that fulfils diverse functions. In both rats and humans five different dopamine receptors have been identified. All these receptors are G-protein-coupled seven-membrane-spanning molecules that modulate the activity of adenylate cyclase, phosphoinositol hydrolysis and intracellular calcium ions.[38,39] In the anterior pituitary the dopamine D_2 receptor predominates and its overall effect is to suppress the synthesis and secretion of prolactin, thyrotropin and GH.[39] Dopamine reaches the pituitary via hypophysial portal blood and can subsequently bind to the D_2 receptors. In addition to inhibiting prolactin release by controlling calcium fluxes, dopamine activates several interacting intracellular signalling pathways and suppresses prolactin gene expression and lactotroph proliferation.[38]

In healthy individuals acute administration of dopamine agonists, such as levodopa, apomorphine, dopamine itself and bromocriptine, causes GH release.[40-42] However, in patients with acromegaly, acute or chronic dopamine agonist treatment inhibits GH secretion.[40,43,44] It is unknown how dopamine agonists exert their action on GH release. It is also unclear how to explain the discrepancy between the action of dopamine agonists on GH release in healthy individuals and patients with acromegaly.

However, considering the fact that dopamine receptors are present on human somatotrophs, the effect of dopamine agonists are most probably exerted directly.[40]

About 20% of all cases of pituitary acromegaly consist of adenomas that express both GH and prolactin.[45,46] Previous data have suggested that these tumours are more likely to respond favourably to treatment with dopamine agonists.[25] Therefore, treatment with dopamine agonists should be considered in acromegalic patients with hyperprolactinaemia, in particular.

Several dopamine agonists are available and have been studied for use in acromegaly: bromocriptine, pergolide, lisuride, quinagolide and cabergoline. These drugs are discussed in sections 2.2 to 2.6. Thereafter, studies comparing the clinical efficacy of two or more dopamine agonists are discussed.

2.2 Bromocriptine

Bromocriptine is a semi-synthetic ergot alkaloid that was introduced for the treatment of hyperprolactinaemia and prolactinomas in 1971.[47] It has been used to treat acromegaly since 1974.[43]

Bromocriptine can bind to both D_1 and D_2 receptors.[48] After oral administration approximately 28% of bromocriptine is absorbed and 90–96% is protein bound. Peak serum concentrations are reached 1–2 hours after ingestion. The elimination half-life is 6–8 hours for the parent drug (initial elimination half-life) and 50 hours for the all metabolites (terminal elimination half-life). Bromocriptine is primarily metabolised via the liver and 98% of the drug is excreted in the faeces, with only trace amounts found in the urine.[49,50]

A number of studies have been performed with respect to clinical use of bromocriptine in acromegaly. These studies are summarised in table I.[51-62] In general, bromocriptine will lead to a reduction in GH levels in most patients. However, among 549 patients from 31 different series, GH levels below 10 and 5 μg/L were reached in 53% and 20%, respectively, and IGF-I levels were normalised in only 10%.[46,50,63] Besides biochemical improvement, bromocriptine can also lead to tumour shrinkage, but this occurred in <20% of recipients.[46,63,64] In order to achieve these results, dosages of 20–30 mg/day in divided doses are necessary (by way of comparison, 2.5–10 mg/day is a usual dose for the treatment of hyperprolactinaemia).[50]

Adverse effects are common, with nausea and orthostatic hypotension being the most common and frequently occurring on initiation of treatment; however, this can be minimised by starting with a small

Table I. Summary of trials of bromocriptine as treatment for acromegaly[47] (reproduced from Vance et al.,[62] with permission; the American College of Physicians is not responsible for the accuracy of any translation of this table)

Study (year)	No. of pts	Dosage	No. of pts with (%)			
		(mg/day)	suppression of GH	GH <5 μg/L	sweating	decreased ring size
Thorner et al.[54] (1975)	11	20	9/11 (82)	0/11	11/11	6/11 (55)
Thorner and Besser[53] (1976)	25	15–60	10/15 (67)	NR	24/25 (96)	17/18 (94)
Wass et al.[52] (1977)	73	10–60	58/73 (79)	15/73 (21)	60/63 (95)	30/34(88)
Belforte et al.[51] (1977)	30	10–20	17/30 (57)	6/30(21)	'Most'	5/14 (36)
Halse et al.[55] (1977)	8	10–20	7/8 (88)	0/8	7/7	7/7
Eskildsen et al.[56] (1978)	14	30–55	10/14 (71)[a]	10/14 (71)[b]	7/9 (78)	7/11 (64)
Lundin et al.[57] (1978)	11	15–40	9/11 (82)	1/11 (9)	7/11 (64)	10/11 (91)
Lindholm et al.[58] (1981)	18	20	6/18 (33)	0/18	NR	NR
Moses et al.[59] (1981)	7	10–40	6/7 (86)	2/7 (29)	NR	6/7 (86)[c]
Nortier et al.[60] (1985)	31	10–20	19/31 (61)	13/31(42)	NR	NR
Tsagarakis et al.[61] (1995)	8	100mg[d]				

a 24-hour urinary levels.

b Urinary excretion <100μg/24h.

c Decrease in shoe size.

d As a monthly intramuscular dose, therefore the other data are not included.

GH = growth hormone; **NR** = not reported; **pts** = patients.

dose (quarter of a tablet) administered at bedtime with a small snack and by gradually increasing the dose (every 3 days) until the effective dose is achieved.[47] Other adverse effects are headache, light-headedness, dizziness, fatigue, nasal congestion, anorexia, vomiting, abdominal cramps, constipation and nasal congestion.[50,62] Arrhythmias, hair loss, insomnia, paranoia and visual hallucinations are less frequently encountered adverse effects.[50,65]

Despite limited biochemical efficacy and frequent occurrence of adverse effects, most patients experience an improvement in clinical symptoms, including decreased soft tissue swelling, decreased ring size and reduced perspiration.[5,46,47]

2.3 Pergolide

Pergolide is a semi-synthetic ergot alkaloid similar to bromocriptine but stated to be more potent (10–1000 times) and longer acting; it is a centrally active dopamine agonist stimulating both D_1 and D_2 receptors.[48,66] Pergolide is believed to exert its therapeutic effect by directly stimulating postsynaptic dopamine receptors in the nigrostriatal system.[66,67]

Pergolide is well absorbed after oral administration and is 90% protein bound in the circulation. It is metabolised by the liver, resulting in an elimination half-life of 27 hours. Excretion is via both the urine and faeces (50% and 50%, respectively).[66]

To the best of our knowledge, only two studies have systematically examined the clinical efficacy of pergolide in the treatment of acromegaly.[68,69] Kleinberg et al.[69] studied seven patients with hypersecretion of GH. After 3 months of pergolide 100 μg/day, the level of GH fell to a mean of 52.8% of baseline in patients with acromegaly.[69] Kendall-Taylor et al.[68] studied the effect of pergolide in eight patients with active acromegaly, none of whom had received pituitary irradiation. In this study much higher doses of pergolide were given compared with the study of Kleinberg et al.[69] All patients showed reduction in GH, although in two, this reduction was not to below 75% of pre-treatment levels. In three patients GH levels of ≤5 mU/L were achieved.[68]

Adverse effects of pergolide mainly relate to the CNS, and include dizziness, somnolence, confusion, hallucinations and dystonia. Other frequent adverse effects are nausea, constipation and postural hypotension.[66]

2.4 Lisuride

Liuzzi et al.[70] have studied the acute effects of a single administration of 0.2–0.4mg of lisuride – an ergot derivative – in 12 patients with acromegaly. GH levels were reduced by more than 50% of the baseline values in only seven of these 12 patients. Two patients were treated with lisuride 0.3mg four times a day for 2 weeks (long-term therapy); in these patients GH and prolactin concentrations were consistently reduced.[70] The effect of long-term treatment was studied in more detail in another study.[71] In 21 patients with acromegaly, lisuride was given in dosages ranging between 0.4 and 2.4 mg/day and GH levels were determined monthly. In ten patients, GH levels were reduced below 10 μg/L; in the remaining patients GH levels were reduced by 50% of the pre-treatment values or remained unchanged. In those patients whose GH was lowered there was also a marked improvement in clinical parameters.[71] Oppizzi et al.[72] also studied the long-term biochemical response of treatment with lisuride on GH secretion in 15 patients with acromegaly. In all patients an acute test with lisuride 0.3mg was performed and, on the basis of GH changes, patients were classified as responders (i.e. reduction in circulating GH concentrations by at least 50% below baseline) or as nonresponders. Treatment was given for 4–26 months (mean ± SE, 13.3 ± 2.8 months). GH levels decreased significantly in those patients with acromegaly who responded to the acute test ($p < 0.001$), but were unchanged in the nonresponders. In addition, there was a significant correlation between the maximal percent GH decrease in the acute test and the response during long-term treatment ($r = 0.73$; $p < 0.01$).[72]

2.5 Quinagolide

Dopaminergic compounds that specifically bind to the D_2 receptor selectively inhibit the binding of quinagolide (CV-205502) to the D_2-receptor agonist. However, compounds specific for the D_1 receptor do not inhibit binding of quinagolide to the D_2 receptor. From these data it can be concluded that quinagolide is indeed a selective D_2-receptor ago-

nist. Because of this selectivity it has been suggested that quinagolide might be superior to bromocriptine in the treatment of patients with acromegaly.

Chiodini et al.[73] were the first to study the effects of quinagolide on GH and IGF-I levels in an open study. After short-term administration of quinagolide (0.0375mg orally) in 12 patients, GH levels did not change, whereas prolactin values significantly decreased and remained suppressed for 24 hours. Long-term treatment with quinagolide was initiated in 14 patients (daily doses of 0.150–0.600 mg/day for up to 12 months), and GH and IGF-I levels fell significantly. A retrospective comparison of the results obtained for the same patients during a previous long-term bromocriptine treatment showed that no bromocriptine-resistant patient was responsive to quinagolide.[73]

In another study, Lombardi et al.[74] studied the potential of quinagolide in therapy-resistant acromegaly. The GH inhibitory effect was evaluated during short-term and 3-month administration. Quinagolide 0.15mg acutely caused a decrease in GH levels (from 34.9 ± 15.1 to 2.7 ± 0.3 μg/L) in 4 of 12 (33.3%) patients and completely inhibited prolactin secretion in all the patients. Administered long-term, quinagolide at the dosage of 0.3 mg/day normalised GH and IGF-I levels in five patients (41.6%: four responders to an acute test and an additional patient who was a poor responder to acute quinagolide administration). Quinagolide was well tolerated by all 12 patients.

2.6 Cabergoline

Cabergoline is a long-acting synthetic ergoline which shows high specificity and affinity for the D_2 receptor.[75] Compared to bromocriptine, cabergoline has a much longer half-life (63–69 hours) and more specific D_2-receptor binding.[75,76] This avoids large fluctuations in dopamine agonist activity, enhances clinical efficacy and reduces adverse effects, at least in patients with hyperprolactinaemia. Time to peak cabergoline concentrations is 2–3 hours, protein binding is 40–42% and it is extensively hepatically metabolised.[76] Adverse reactions are mainly headache (26%), dizziness (17%) and nausea (29%).[75,76] Because much higher doses are required in acromegaly than in the treatment of hyperprolactinaemia, these pharmacological characteristics may be of even greater importance.

In a recent multicentre, prospective, open-labelled study from Belgium, Abs and coworkers[24] evaluated the effect of long-term administration of cabergoline in 64 unselected patients with acromegaly.[24] Sixteen patients had mixed GH-prolactin-secreting pituitary adenomas. Treatment with cabergoline suppressed plasma IGF-I to below 300 μg/L in 39% of patients and between 300 and 450 μg/L in another 28%. An important finding was that in patients with relatively low pre-treatment serum total IGF-I, as well as in those patients with mixed GH-prolactin secreting pituitary adenomas, cabergoline was especially effective in reducing IGF-I to within the normal range. With pre-treatment plasma IGF-I levels <750 μg/L, a suppression of IGF-I below 300 μg/L was obtained in 53% of patients. In contrast, in those with pre-treatment plasma IGF-I levels >750 μg/L, only 17% showed a suppression of IGF-I below 300 μg/L. In patients with mixed GH-prolactin-secreting pituitary adenomas 50% of patients had plasma IGF-I levels suppressed to below 300 μg/L. However, only 30% of patients with GH-secreting adenomas achieved normalised IGF-I levels. Similar results were obtained regarding the secretion of GH. Tumour shrinkage was demonstrated in 13 of 21 patients, with a mass reduction by more than half in five mixed GH-prolactin-secreting pituitary adenomas. Except for slight gastrointestinal discomfort and orthostatic hypotension in a few patients at the beginning of therapy, cabergoline treatment was well tolerated. The weekly dose of cabergoline ranged between 1.0 and 1.75mg. A further increase in the dose was only effective in one GH-prolactin-secreting pituitary adenoma.

On the basis of these findings, cabergoline can be considered as treatment in those patients in whom a mixed GH-prolactin-secreting pituitary adenoma is present or in those patients in whom pre-treatment IGF-I concentrations are <750 μg/L.

2.7 Summary

In patients with prolactinomas, quinagolide and cabergoline have been compared in terms of efficacy and tolerability.[77-80] Collectively, these studies indicate that cabergoline is more efficacious in the treatment of hyperprolactinaemia. Unfortunate-

ly, comparative data between quinagolide and cabergoline with respect to acromegaly are scarce.

One study by Colao et al.[81] reported on a comparison of long-term treatment with quinagolide or cabergoline, as well as the now unavailable long-acting bromocriptine depot preparation. Quinagolide, cabergoline and bromocriptine all caused a significant decrease in GH, IGF-I and prolactin. In 44% of the patients treated with quinagolide, GH and IGF-I normalised; in contrast, no patient treated with cabergoline or bromocriptine attained normalised GH and IGF-I levels. In this study, the percentage of suppression during quinagolide treatment was significantly greater than that obtained during long-term cabergoline treatment. All 34 patients in this study reported marked clinical improvement. Only two patients treated with quinagolide and one treated with bromocriptine showed significant adenoma shrinkage. Visual field defects and visual acuity improved in all four patients with visual abnormalities.

Considering all of the studies on dopamine agonists together, we have concluded that this class of drugs cannot be considered as medical treatment of choice simply because only a minority of patients achieve normal circulating GH and IGF-I levels. Moreover, more effective treatments are widely available (see sections 3 and 4). However, in a subset of patients (namely those in whom a mixed GH-prolactin-secreting pituitary adenoma is present and/or those in whom pre-treatment IGF-I concentrations are <750 μg/L) dopamine agonists – especially cabergoline – can be considered as the primary medical treatment.[24] Dopamine agonists also have the advantage of being orally administered and relatively inexpensive compared with somatostatin antagonists and pegvisomant.

3. Somatostatin Analogues

3.1 Introduction

Somatostatin was discovered in 1973 by Guillemin and Gerich.[82] Somatostatin is an acyclic peptide of 14 amino acids (SS-14), but there is also a longer form of 28 amino acids (SS-28). Since 1973 knowledge of the functional role of somatostatin as a brain neurotransmitter, as well as in the regulation of secretion processes in the anterior pituitary gland, the pancreas and the gastrointestinal tract, has increased considerably.[83,84] Besides an important regulatory role in neurotransmission and secretion, the peptide may also control cell proliferation in normal and tumorous tissues.[83,85] The different actions of somatostatin are mediated via specific membrane receptors. The presence of these somatostatin receptors has been demonstrated in the brain, anterior pituitary, endocrine and exocrine pancreas, gastrointestinal tract mucosa and tissues involved in the immune system.[86-90] Between 1992 and 1994, five somatostatin receptor subtype genes were cloned and characterised; they were code named *sst1*, *sst2*, *sst3*, *sst4* and *sst5*.[91] These subtypes belong to a superfamily of receptors with G-protein-coupled seven-membrane-spanning molecules that modulate the activity of adenylate cyclase.[39,84] Subsequent studies have elucidated the expression in somatostatin receptor subtypes in somatostatin target tissues as well as their selectivity of binding of somatostatin analogues.[92,93] The expression of somatostatin receptor subtypes has recently been reviewed by Hofland and Lamberts.[94]

3.2 Somatostatin Receptor Subtypes and their Preferred Analogues

Currently, several somatostatin agonists are known to exist, each with different affinities for the respective somatostatin receptor subtypes (figure 1). Regarding somatotroph adenomas, somatostatin receptor (SSTR) subtype-2 (SSTR2) is expressed in 96% of tumours and SSTR5 is expressed in 86% of tumours[94] (figure 2). On the basis of the above described data it seems logical to hypothesise that the efficacy of a given somatostatin analogue depends on two factors: (i) the number and subtypes of somatostatin receptors that are present on the target tissue (i.e. the somatotroph adenoma in case of acromegaly); and (ii) the affinity of the analogue for the subtypes present on the target tissue. Indeed, Reubi and Landolt[95] have shown that the short-term suppression of GH in response to a somatostatin analogue in patients with acromegaly depends on the number of somatostatin receptors present on the somatotroph adenoma. Octreotide, the first somatostatin analogue introduced for clinical use, inhibits the release of GH in monkeys 45-fold more than

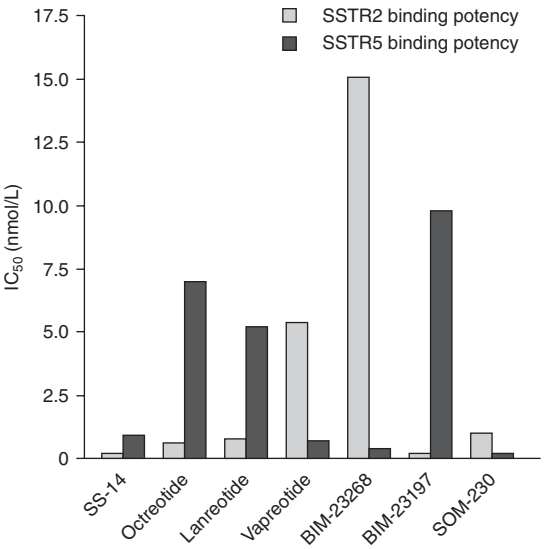

Fig. 1. Affinities of somatostatin analogues for somatostatin receptor (SSTR) subtypes.[89,98-101] **IC_{50}** = concentration that produces 50% inhibition.

somatostatin-14, indicating that receptor subtype affinity plays a role as well.[96] However, with prolonged administration of somatostatin analogues the large number of mainly inhibitory effects diminishes – a phenomenon called adaptation or tachyphylaxis.[94] Several mechanisms are potentially involved in this process such as receptor phosphorylation, G-protein uncoupling, receptor internalisation and degradation.[94] At this point it should be emphasised that in patients with acromegaly tachyphylaxis has been observed only extremely rarely and should therefore be of no concern to the clinician.[94,97]

Somatostatin analogues may be divided in two groups. First, those somatostatin analogues that have a high affinity for SSTR2, such as octreotide and lanreotide. The experimental somatostatin analogues BIM-23023, BIM-23190 and BIM-23197 also belong to this group. Secondly, those analogues with increased binding affinity for SSTR5. Members from this group are still in development and include, among others, BIM-23268 and BIM-23052. Another new strategy is to develop compounds with a high affinity to all five somatostatin receptor subtypes.[98,106] Recently, a new somatostatin analogue, SOM 230, has been developed, that has high affinity for SSTR1, SSTR2, SSTR3 and SSTR5 receptors.[98,106] In a recent single-dose study SOM 230 250μg was at least as effective as octreotide 100g with regard to acute GH suppression.[107] It is hoped that the further development of analogues with increased binding affinity to several somatostatin receptor subtypes will result in opportunities to better control GH hypersecretion in patients with acromegaly, and at the same time will also lead to adenoma regression.

3.2.1 GH Secretion

Clinical experience and previous cell culture studies of acromegalic tumours have shown that somatostatin agonists can have variable effects on GH secretion.[108-110] In a recent study, Jaquet and coworkers[111] investigated this phenomenon by studying the differential effects of SSTR2- and SSTR5-preferring compounds. They analysed the GH and prolactin inhibitory effects of SS-14, octreotide, the SSTR2 preferential compound BIM-23197 and the SSTR5 preferential compound BIM-23268 in cells cultured from 15 somatotroph adenomas.[111] Reverse transcriptase polymerase chain reaction (RT-PCR) showed a constant co-expression of SSTR2 and SSTR5 mRNA in adenomas from all patients. Despite individual variations, the relative expression of SSRT2 and SSTR5 was similar in the tumours secreting GH alone or both GH and prolac-

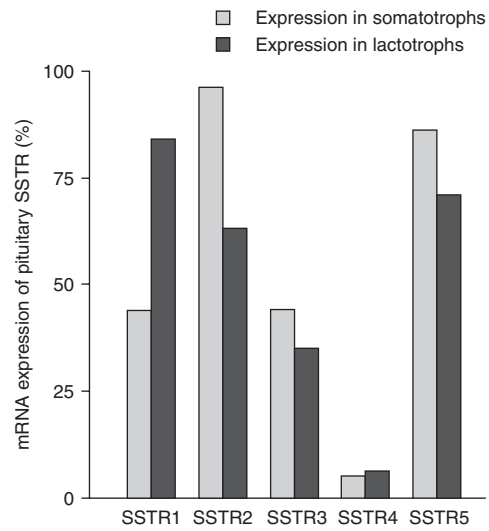

Fig. 2. Messenger RNA (mRNA) expression of somatostatin receptor (SSTR) subtypes (1–5) in the pituitary.[88,102-105]

tin, but the mean level of SSTR5 mRNA expression was consistently much higher than that of the SSTR2 transcript. However, only SSTR2 mRNA expression correlated with the degree of GH inhibition induced by SS-14, SS-28 and BIM-23197. The SSTR5 preferential compound inhibited GH release in only 7 of 15 adenomas. In cells cultured from the ten adenomas that co-secreted GH and prolactin, RT-PCR analysis revealed a consistent co-expression of SSTR5, SSTR2 and SSTR1 mRNA. In all cases SS-14, SS-28 and the SSTR5-preferential analogue, BIM-23268, showed a significantly suppressed prolactin secretion. In contrast, the SSTR2 preferential analogues, BIM-23197 and octreotide, were effective in suppressing prolactin in only six of ten patients. Interestingly, in cells cultured from adenomas taken from patients partially responsive to octreotide, partial additivity in suppressing both GH and prolactin secretion was observed when the SSTR2 and SSTR5 preferring analogues, BIM-23197 and BIM-23268, were tested in combination. In conclusion, the SSTR-preferring compound consistently inhibits GH release, whereas the SSTR5-preferring compound is the main inhibitor of prolactin secretion. When both drugs are combined, the partial additivity observed in mixed GH- plus prolactin-secreting adenomas may be of interest in the therapeutic approach of such tumours. This is an important study in that it adds to the understanding of the variable suppressive effects that somatostatin agonists can have on GH secretion, according to the individual nature of each tumour.

3.2.2 Adenoma Growth

With regard to tumour growth, Danila et al.[112] have studied the effects of somatostatin and its analogues on pituitary tumour proliferation as well as the relationship between the effects of somatostatin analogues on GH secretion and tumour cell proliferation and, finally, whether somatostatin receptor subtype expression predicts the antiproliferative effects of somatostatin analogues in human somatotroph tumours.[112] They studied the effects of somatostatin-14, lanreotide and the SSTR2-preferring analogue BIM-23190 and SSTR5-preferring analogue BIM-23268 in 18 somatotroph pituitary adenomas in primary culture. Interestingly, they observed dissociation between the *in vitro* effects of somatostatin-14 and lanreotide on tumour cell proliferation, and the effects on GH secretion in human somatotroph tumours. Although differences in receptor concentration and the presence of other somatostatin receptor subtypes may play a role, the presence of SSTR2 and SSTR5 did not have a predictive value, suggesting that inhibition of cell proliferation occurs independently of effects on GH secretory pathways. Whereas the study of Jaquet et al.[111] described in section 3.2.1 helps to explain the variable suppressive effects that somatostatin agonists can have on GH secretion, this study confirms other observations of the dissociation between the effects of somatostatin on GH secretion and tumour size in somatotroph adenomas.[113]

3.3 Pharmacological Characteristics

The clinical use of the native somatostatin peptide is hampered by its short half-life in the circulation (a few minutes),[39] and so longer acting and selective somatostatin analogues (octreotide, lanreotide, vapreotide) have been developed.

Subcutaneously administered octreotide was the first preparation available for clinical use.[31] Octreotide levels rise within 30 minutes after injection and then fall over a few hours.[31] The maximal suppressive effect of octreotide on GH levels occurs 2–6 hours after injection.[31,114] A typical dose administration regimen of subcutaneous octreotide consists of 100–250μg three times daily; however, if necessary, daily doses of up to 1500μg can be given.[31,115] GH levels rise between injections given every 8 hours but with continued treatment this rise is lessened.[31,116] Therapy should be initiated with a dose of 100μg subcutaneously every 8 hours. If GH secretion is not reduced substantially, the dose can be increased gradually to 500μg three times daily.[63]

A long-acting release (LAR) octreotide formulation has been synthesised in which 20–30mg of octreotide is enclosed in microspheres of slowly biodegradable DL-lactide-co-glycolide polymer allowing for prolonged release.[117] After intramuscular injection of octreotide LAR, octreotide concentrations rise briefly then fall and begin to rise again after 7–14 days, remaining elevated for an average of 34 days.[118] After two to three injections a steady state ensues.[31,118,119] This long-acting repeatable intramuscular depot preparation of octreotide is well tolerated and effectively controls hormonal hyper-

secretion in most patients with acromegaly for 28–42 days. Therefore, in some patients the dose administration interval may be prolonged to 6–8 weeks, as opposed to the monthly interval that is recommended by the manufacturer.[31,120,121]

Before a long-acting somatostatin analogue is prescribed, the serum GH response of the patient to a short-acting formulation should be assessed. Patients who have never received a short-acting somatostatin analogue should be given a single subcutaneous injection (100μg) and serum GH should be measured before and 4 hours after administration. If the serum GH level is <50% of baseline, administration of the long-acting formulation is warranted.[63,122]

The slow-release (SR) intramuscular formulation of lanreotide, which is also bound to lactide-glycolide copolymers in quantities of 30 and 60mg, also effectively controls GH levels in patients with acromegaly. However, its duration of action is 2 weeks at most, necessitating a dose administration interval of 10–14 days.[31,123] As with octreotide LAR, this dose administration interval may need to be decreased or can be increased in some patients.[31,121]

Another long-acting formulation of lanreotide, in which lanreotide (60, 90 or 120mg) is subcutaneously administered in a translucent semi-solid form (autogel) is available in most of Europe, although still not available in the US. In clinical studies, this formulation has shown to effectively control GH hypersecretion for at least 4 weeks in patients with acromegaly.[124,125]

3.4 Clinical Efficacy

As long-acting formulations are now available and most likely to be chosen in clinical practice, this section only discusses the efficacy of currently available long-acting depot somatostatin analogues. It is sufficient to say that several studies have compared the efficacy of subcutaneous octreotide versus the long-acting preparations and have reported similar efficacy.[126-130]

3.4.1 Biochemical Control

Somatostatin analogues are known to be effective in normalising IGF-I levels in about two-thirds of acromegalic patients (figure 3).[27,28,117,118,123,126-138] Long-acting formulations were able to normalise GH levels in about 50% of patients (figure 3).[27,28,117,118,123,126-138] However, only 6% of the patients in these studies had had no previous therapy.[31] Previous therapy consisted of surgery in 69%, radiotherapy in 33% and subcutaneous octreotide therapy in 70%.[31] In addition, in these studies most patients were preselected for octreotide responsiveness.[31]

In a number of studies biochemical efficacy of octreotide LAR and lanreotide SR have been compared.[26,140-142] In the largest of these studies, Chanson et al.[26] compared the efficacy of octreotide LAR and lanreotide SR in 125 patients with acromegaly. Before the study, all patients had been treated with intramuscular injections of lanreotide SR (mean duration 26 months) at a dose of 30mg, which was injected every 10 days in 64 and every 14 days in 61 patients, respectively. All patients were switched from lanreotide SR to intramuscular injections of octreotide LAR 20mg once monthly for 3 months. The percentages of patients with mean GH values <2.5 and 1.0 μg/L during lanreotide SR therapy were 54% and 14%, respectively, while these

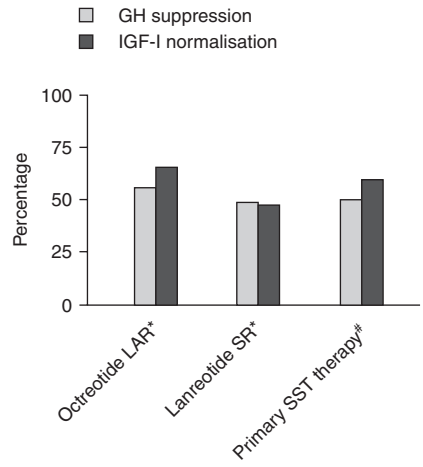

Fig. 3. Biochemical efficacy of somatostatin (SST) analogue therapy for acromegaly. Growth hormone (GH) suppression defined as: GH level of <2.0 or 2.5 μg/L on random or mean of hourly sampling or <1.0 μg/L after oral glucose suppression.[27,28,117,118,123,127-139] **IGF-I** = insulin-like growth factor-I; **LAR** = long-acting release; **SR** = slow release; * indicates previous therapy included surgery in 69%, radiotherapy in 33%, subcutaneous octreotide therapy in 70% (approximately 6% had no prior therapy); # indicates data with subcutaneous octreotide, octreotide LAR and lanreotide SR.

values increased after 3 months' treatment with octreotide LAR to 65% and 35% ($p < 0.001$), respectively. IGF-I levels were normal in 48% at the last evaluation on lanreotide SR, and in 65% after 3 months on octreotide LAR ($p < 0.001$). This large multicentre study can be interpreted as demonstrating that octreotide LAR 20mg administered monthly is more effective than lanreotide SR administered two or three times monthly in reducing GH and IGF-I in patients with acromegaly. These data are in accordance with the other studies comparing octreotide LAR with lanreotide SR.[140-142]

No comparative studies between octreotide LAR and the newest application form of lanreotide (lanreotide autogel) are available to date.

3.4.2 Tumour Shrinkage

Overall, somatostatin analogues result in tumour shrinkage in 30% of patients (figure 4).[28,31,117,123,128,130,131,134-138] Most frequently, tumour shrinkage was between 20% and 50%. However, several factors suggest that we should review these numbers cautiously. Tumour shrinkage data are available from studies in which approximately 90% of patients treated with octreotide LAR and some 10% of patients treated with lanreotide SR were preselected for octreotide responsiveness.[31] Moreover, radiotherapy and a relatively short follow-up period of 3–4 years may play a role.[31]

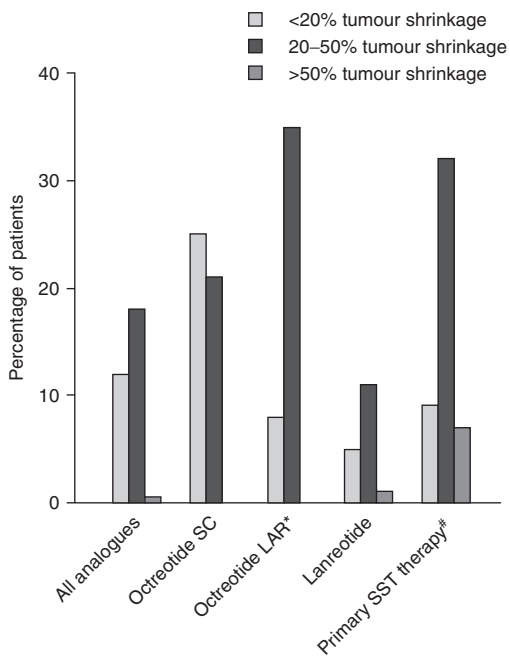

Fig. 4. Tumour shrinkage in patients with acromegaly receiving somatostatin (SST) analogue therapy.[28,117,118,123,127-131,133-139,143-150] **LAR** = long-acting release; **SC** = subcutaneous; * indicates previous therapy included surgery in 69%, radiotherapy in 33%, SC octreotide therapy in 70% (approximately 6% had no prior therapy); # indicates data with SC octreotide, octreotide LAR and lanreotide SR.

In patients receiving somatostatin analogues as primary therapy in these trials, only 6% were preselected on the basis of octreotide responsiveness (see figure 4 and section 3.2.2).[31,127,129,130,143-147]

3.4.3 Pre-treatment of Acromegalic Patients Before Neurosurgery

It has been reported that pre-treatment with somatostatin analogues in patients with acromegaly improves surgical cure rates, although data in the literature are conflicting. Another rationale for perioperative treatment of patients with acromegaly is that the complications of acromegaly – cardiovascular, respiratory and metabolic – are well known risk factors for perioperative morbidity and mortality.[151,152] Therefore, it seems logical that controlling these factors has a favourable effect on the outcome of surgery for acromegaly.

Before discussing the possible effects of pre-treatment with somatostatin analogues on surgical outcome it is relevant to realise what the results of surgery without pre-treatment are. In centres of excellence, approximately 90% of patients with microadenomas and 50% of patients with macroadenomas are considered cured by the criteria described in section 1.4.[37,151,153]

A recent review by Ben-Shlomo and Melmed[151] summarised several studies considering perioperative treatment.[151] There are currently no studies that have systematically studied whether tumour shrinkage before surgery facilitates complete resection; therefore, this question cannot be answered.[151] Particularly in patients with a microadenoma, somatostatin pre-treatment does not seem beneficial for the already excellent outcomes of surgery.[151] Conversely, in patients with macroadenomas a case can be made for pre-treatment.[151]

Another issue pertains to perioperative morbidity. During surgery, patients with acromegaly experience more problems than sex- and age-matched

controls.[151,154] However, in most studies, treatment with somatostatin analogues improves at least some of cardiac indices assessed.[151,155-162] In addition, the occurrence arrhythmias is decreased by somatostatin treatment.[143,151] Pulmonary function, upper airway soft tissue swelling and symptoms associated with sleep apnoea are also positively influenced by treatment with somatostatin analogues.[151,163-167]

Finally, patients pre-treated with long-acting somatostatin analogues may be inappropriately considered as cured when the postoperative hormonal evaluation is completed too soon after the last injection.

Considering these findings, perioperative treatment with somatostatin analogues might very well be considered; however, it should be stressed that prospective controlled studies are lacking.

3.4.4 Primary Medical Therapy for Acromegaly

Not all patients are able or willing to undergo pituitary surgery. A lowering of GH and IGF-I levels and variable effects of adenoma growth have been observed during preoperative treatment with somatostatin analogues.[143,148,168] Several authors have reported on the effects of octreotide in previously untreated patients with acromegaly.

On the basis of these data the concept of primary medical therapy has been investigated more systematically.[131,145,146,169] In the two most recent studies, tumour shrinkage occurred in a substantial number of patients. Colao et al.[131] observed a decrease in tumour volume in 12 of 15 previously untreated patients, whereas no shrinkage was detected in four of nine patients who had had surgery. No patient had tumour re-expansion during treatment with octreotide LAR.[131] However, in the study by Bevan et al.[169] 73% of the 27 patients studied showed >30% tumour shrinkage. These authors have also pointed out some of the difficulties that can occur when analysing tumour volume.

In both studies, GH control was achieved in approximately 75% of patients and 53% achieved normal IGF-I levels.[131,169]

3.5 Summary

Somatostatin analogues are capable of achieving biochemical control of GH and IGF-I in 50–60% of patients and tumour shrinkage in some 30%. Moreover, adverse effects are often transient and seldom a reason to discontinue therapy.[31] Frequently observed adverse effects are nausea, abdominal discomfort, bloating, loose stools and fat malabsorption; in most patients these are transient, occurring in the first weeks of therapy.[84] Also, mild glucose intolerance can occur because of impairment in insulin secretion,[84] and as a result of impaired gallbladder emptying approximately one-quarter of patients develop asymptomatic gallstones or sludge during the first 18 months of therapy.[165,170] Candidates for treatment with these compounds are, in particular, those patients who underwent an unsuccessful transsphenoidal operation or who await the therapeutic effect of external pituitary irradiation. In selected patients primary medical therapy is certainly a feasible option.

4. Growth Hormone (GH) Receptor (GHR) Antagonists

4.1 Introduction

Early studies by Clemmons et al.[171] utilising high-dose estrogen therapy and by Ho et al.[172] investigating the effects of fasting on the GH–IGF-I axis showed that it is possible to reduce IGF-I levels in patients with acromegaly without affecting circulating GH levels. Although these interventions were clinically impractical, these studies have provided proof of principle that disrupting the function of the GHR, rather than attempting to destroy the tumour itself or impairing its secretory capacity, might treat acromegaly.

To date, pegvisomant is the only available member of a new class of drugs specifically designed to block the GHR and, therefore, GH action.

Before discussing the available clinical data we describe the structure and function of GH and its receptor with specific relevance to the development of pegvisomant.

4.2 Development of Pegvisomant

4.2.1 GH – GHR Interaction

The GHR is a transmembrane receptor and consists of an intracellular and an extracellular domain linked by a transmembrane domain of 20–30 amino acids.[173] The extracellular domain of the GHR is

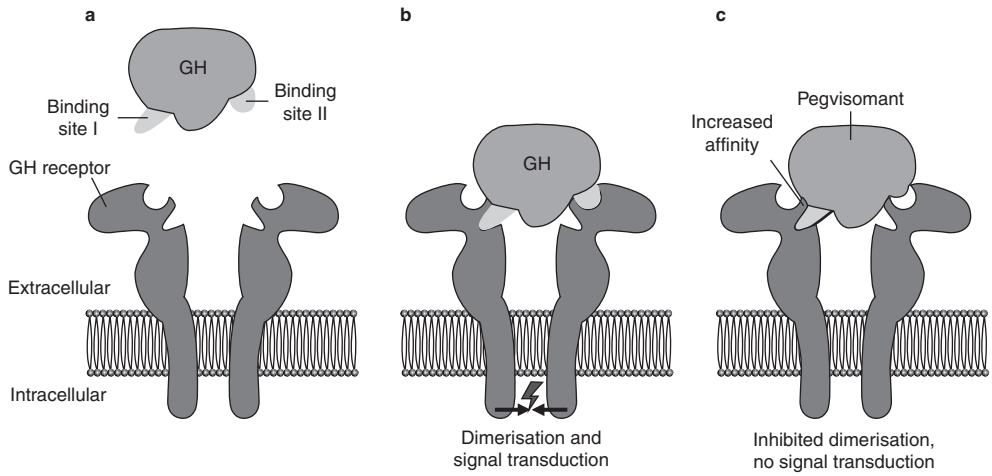

Fig. 5. Mode of action of pegvisomant. (**a**) Normally growth hormone (GH) binds to the first GH receptor (GHR) with binding site I; (**b**) the subsequent binding of binding site II to the second GHR results in receptor dimerisation and signal transduction; (**c**) eight mutations at binding site I increase the affinity of pegvisomant for the GHR and one mutation at binding site II inhibits receptor dimerisation and, thus, signal transduction.[178]

also present in serum, where it acts as a GH binding protein.[174] Binding of GH to the GHR is necessary for signal transduction. It has been shown that dimerisation of GH with two GHRs is critical for signal transduction to occur.[175-177] GH has two distinct binding domains that bind to two identical GHRs at the cell surface. Following the initial (high affinity) binding of the so-called GH binding site I at the GHR, sequential binding at GH site II produces functional receptor dimerisation and signal transduction, for example, leading to IGF-I generation (figure 5a and b).

The importance of receptor dimerisation in signal transduction is indicated by a number of experiments. High concentrations of GH, which favour the monomeric GH-GHR complex, inhibit the GH signal.[179] Truncated receptors lacking the cytoplasmic domain act as dominant negative inhibitors of signalling by heterodimerisation with the full-length receptor.[180] Mutations in the inter-receptor dimerisation domain inhibit signalling without influencing GH binding.[181] Finally, the strongest evidence comes from work with a GH molecule mutated at site II to prevent receptor dimerisation.[179,182-185] These GH mutants block GH-stimulated cell proliferation, the conformational change associated with receptor dimerisation, and Jak-Stat signalling.[186]

4.2.2 Pegvisomant

The understanding of the mechanism by which GH interacts with its receptor has facilitated the development of pegvisomant (figure 5c).[187] Through a single mutation at site II of the GH molecule functional GHR dimerisation is inhibited. Moreover, to increase the binding affinity of the GHR antagonist and thus provide the GHR antagonist with a (pharmaco)kinetic advantage compared with endogenous GH, eight amino acids at binding site I were also mutated.[179,182,188] Pegvisomant is pegylated to increase serum half-life and to reduce the likelihood of antibody formation. It was argued that the GHR antagonist with eight amino acid substitutions in GH site I would result in molecules that would bind to the GHR with increased affinity. However, of the eight amino acid changes made within binding site I, two (namely lysine to alanine and lysine to arginine at positions 168 and 172, respectively) are nevertheless critical with regard to site I binding of the pegylated antagonist. Pegylation at these lysine residues would block or sterically hinder binding of the antagonist to the first GHR. Substitution of these residues removes potential pegylation sites within binding site I and, thus, ensures that site I of pegvisomant remains accessible to the GHR.[181,187]

Nevertheless, pegylation of the antagonist does reduce site I binding affinity and, thus, large doses of pegvisomant are required to effectively antagonise GH action and suppress IGF-I production in patients with acromegaly.[189]

4.3 Clinical Efficacy

4.3.1 Biochemical Control

In a 12-week, double-blind, placebo-controlled study pegvisomant significantly improved both the biochemical and clinical parameters of acromegaly.[190] All patients treated with pegvisomant had their serum IGF-I reduced from baseline in a significant, dose-dependent fashion compared with placebo. Patients treated with the highest dose of pegvisomant in this study (20 mg/day) had a mean reduction in IGF-I of 64%, with 89% of patients achieving a normal IGF-I value at any time during the course of the study and 85% achieving a normal IGF-I at week 12. Besides IGF-I levels, a questionnaire evaluating soft tissue swelling, arthralgia, headache, excessive perspiration and fatigue was used to assess efficacy. In the pegvisomant-treated patients a dose-related improvement in symptoms and signs was observed.

Serum GH levels increase substantially during pegvisomant therapy.[190] This raises the question of whether additional increases in serum GH levels might occur during prolonged treatment, as well as whether a sustained increase in serum GH levels might overcome the receptor blocking action of the drug (i.e. induce tachyphylaxis). Experimental data suggest that the observed increase in GH levels in both patients with acromegaly and in healthy individuals is likely to be due to an increase in release and/or production.[191,192] Lamberts and coworkers[193] demonstrated that both IGF-I and octreotide directly inhibit GH release during a 24-hour incubation in, respectively, four and five of seven primary tumour cell cultures prepared from GH secreting pituitary adenomas.[193] Apparently, many GH-secreting adenomas remain sensitive to the negative feedback effect of IGF-I. It is probable that the decreased serum IGF-I levels induced by the presence of pegvisomant result in a diminished negative feedback of IGF-I on GH release by the pituitary adenoma. This is further supported by the observation that, in patients with acromegaly who are treated with pegvisomant, the rise in mean serum GH levels mirrors the fall in serum IGF-I levels.[187,190,194] Also, GH levels increase during the first 2–4 weeks of pegvisomant therapy but do not continue to increase progressively.[190] In a subgroup of patients (n = 45) who were withdrawn from pegvisomant and not placed on alternative medical therapy for 1 month, the serum GH levels decreased to baseline levels, which again strongly suggests that increases in GH levels during long-term pegvisomant therapy are the result of a decrease in the negative feedback effect of high IGF-I levels.

A report by Herman-Bonert and coworkers[195] describes six patients who were resistant to maximal doses of octreotide therapy. These patients received daily pegvisomant injections at doses determined by titrating IGF-I levels. An important finding of this study was that serum IGF-I levels were normalised in all six of these patients with acromegaly, who were previously shown to be resistant to somatostatin analogues. Other metabolic consequences of acromegaly may also be improved by blocking the GHR with pegvisomant.[196]

In conclusion, although pegvisomant seemed a very effective drug for the treatment of acromegaly, questions concerning safety and efficacy in the long-term remained.[190,197] Specifically, there was the concern that the increase in GH might be accompanied by growth of the pituitary tumour.[197] To address these questions concerning long-term efficacy and safety, the study was extended to include 152 patients with acromegaly who were treated for up to 18 months.[194] In this study, pegvisomant was administered by daily subcutaneous injection and titrated until the serum IGF-I level became normal or a maximum dose of 40 mg/day was reached. Of patients treated for 12 months, 97% (i.e. 87 of 90) achieved normal IGF-I levels.[194]

4.3.2 Safety

Fortunately, for 131 patients with adenomas of >1 cm^3, paired sets of baseline and follow-up scans (mean time between scans 11.46 months) did not show a significant increase in tumour volume.[194] In these patients, the mean duration of pegvisomant treatment at the time of the most recent scan was 1 year, ranging from a minimum of 6 weeks to a maximum of 2.5 years. There was no association

between size of the tumour and change in tumour volume while on pegvisomant therapy, nor was there an association between the duration of pegvisomant treatment and change in tumour volume.[194] On the other hand, two patients, who were not pre-treated with radiotherapy, demonstrated a clinically significant increase in tumour size.[194] Both had already large, globular tumours with impingement on the optic chiasm at baseline. Interestingly, in one of these patients co-treatment with octreotide halted further tumour growth and resulted in a synergistic decrease in serum IGF-I levels.[189] Therefore, in patients shown to have aggressive disease and significant residual tumour, pre-treatment with radiotherapy should be seriously considered. Another two patients developed a significant, but reversible, increase in serum liver enzyme levels in the first 3 months after starting pegvisomant. One of these patients was rechallenged and on this occasion liver enzymes rose again.[194] On the basis of these data it is currently advised that patients receiving pegvisomant should have liver function tests monitored once a month during the first 6 months of treatment and should have adenoma size assessed by magnetic resonance imaging (MRI) once a year.[63]

4.4 Summary

Pegvisomant therapy appears to be well tolerated. However, the observation that two patients experienced elevations of liver enzymes requiring discontinuation of the drug, with a positive rechallenge in one, suggests that caution is warranted and that liver function tests should be regularly monitored until a larger number of patients have been exposed to the drug. In addition, tumour size should be closely followed to detect possible (re)growth of the somatotropinoma during long-term pegvisomant therapy.

Interestingly, 11 of the 90 patients treated for more than 1 year had serum IGF-I levels that fell below the lower limit of the age-adjusted normal range. These findings suggest that in order to prevent over treatment, IGF-I must be monitored frequently and the pegvisomant dose adjusted to keep the serum IGF-I levels within the normal range.

5. Considerations for Medical Treatment of Acromegaly

Several issues should be addressed when comparing medical treatment modalities: biochemical control, clinical disease activity, long-term safety (including control of tumour size) and mode of administration.

5.1 Biochemical Control

Dopamine agonists, especially cabergoline, can be considered as primary therapy in a subset of patients; namely, those in whom a mixed GH-prolactin-secreting pituitary adenoma is present and/or those in whom pre-treatment IGF-I levels are <750 μg/L.[24] Somatostatin analogues are known to be effective in normalising serum IGF-I levels in patients with acromegaly in approximately two-third of patients. Lombardi et al.[74] have investigated the additional effect quinagolide in patients who, despite previous surgery and long-term therapy with octreotide, still have high GH and IGF-I levels. In this study seven patients received co-treatment with quinagolide in higher dosages (0.6 mg/day) and octreotide (0.6 mg/day) in combination for 3 months. In two of seven patients, the combined therapy induced a greater inhibition of GH and IGF-I levels than did each drug when administered alone.[74]

Pegvisomant is able to reduce serum IGF-I levels in virtually all patients with acromegaly. Thus, with regard to biochemical control (i.e. normalisation of IGF-I), pegvisomant is superior to any available treatment whether surgical or medical. However, it should be realised that during GHR blockade, GH levels are of no value as a parameter to assess disease activity. As no studies are available on morbidity and mortality using IGF-I values as parameter, it will be difficult to compare long-term safety data on pegvisomant therapy versus other treatment modalities.

Another issue is that we do not know whether the future availability of somatostatin analogues, with higher affinity to both SSTR2 and SSTR5, will increase the efficacy of somatostatin analogues to normalise serum IGF-I levels.

5.2 Clinical Disease Activity

During treatment with bromocriptine, despite frequent occurrence of adverse effects, most patients experience an improvement in clinical symptoms, including decreased soft tissue swelling, decreased ring size and reduced perspiration.[5,46,47]

Strangely, and despite the huge amount of safety data and the well known clinical experience of many clinicians, no comparative data on the improvement of clinical disease activity of patients with acromegaly while being treated with different somatostatin analogues exist. However, in 64–74% of patients treated with a long-acting somatostatin analogue, signs and symptoms show some improvement.[118,126,127,129,132,133,135,137,138]

Pegvisomant treatment induced a clearcut improvement in clinical signs and symptoms.[190,194] These improvements could be demonstrated within 3 months of therapy and are also dose dependent.[190,194]

5.3 Long-Term Safety

Bromocriptine and somatostatin analogues can be considered well tolerated with good safety profiles. Dopamine agonists and somatostatin analogues can induce tumour shrinkage in 20–30% of patients.[31,46,63,64] Safety data on pegvisomant are scarce and obviously limited with respect to years of follow-up. However, clinical experience with pegvisomant now extends to an accumulated 186 patient-years of exposure, with each patient being treated for an average of more than 400 days. One item with a potential concern with regard to safety is the observation of clinically important liver function abnormalities in two patients. Therefore, it is advocated that liver function tests should be monitored on a regular basis during long-term treatment with pegvisomant.

The data on tumour growth and pegvisomant have been discussed in section 3.3.2; the question remains as to whether pegvisomant treatment interferes with the natural history of these GH-producing tumours or if pegvisomant in fact induces an increase in tumour size by increasing GH secretion.

5.4 Mode of Administration

Dopamine agonists can be administered orally. Both somatostatin analogues and pegvisomant have to be administered either subcutaneously or intramuscularly. Daily injections are required with pegvisomant, although its half-life of more than 120 hours should allow a longer between-injection interval. However, as trough concentrations are higher when pegvisomant is given daily instead of weekly, the efficacy of daily injections has been proven to be superior to weekly administrations.[194] Both octreotide LAR and lanreotide SR must be administered intramuscularly at intervals of 4 weeks or 7–14 days, respectively. When lanreotide autogel becomes available, lanreotide will also be able to be given once monthly. The advantage of lanreotide autogel is that patient can administer it themselves, as it can be given subcutaneously instead of intramuscularly.

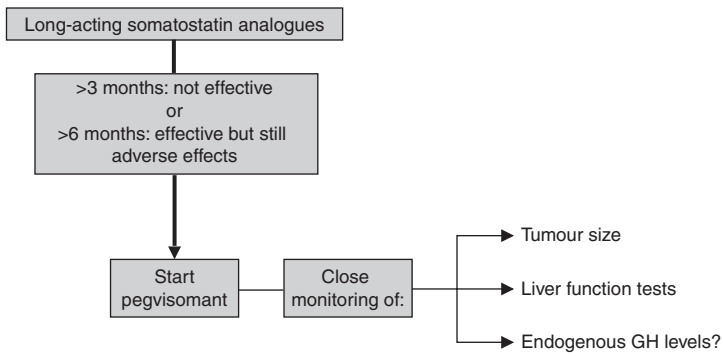

Fig. 6. Proposed pharmacological treatment of acromegaly. **GH** = growth hormone.

6. How to Proceed with Pharmacological Treatment of Acromegaly

In conclusion, a pharmacological treatment algorithm is presented here and summarised in figure 6.

Somatostatin analogues are currently considered to be treatment of choice for those patients with acromegaly in whom medical treatment is indicated. Although the available somatostatin analogues are less effective than pegvisomant in normalising serum total IGF-I levels, they possess a safety record that makes them first-line medical treatment (see figure 6).

In those patients with acromegaly in whom serum IGF-I levels are relatively low and/or when GH and prolactin are co-secreted, dopaminergic compounds (especially cabergoline) should be considered as these drugs can be administered orally and are inexpensive.

When treatment with somatostatin analogues does not result in a clinically significant reduction in serum IGF-I levels, pegvisomant should be started and somatostatin treatment stopped. Patients receiving pegvisomant should have liver function tests monitored once a month during the first 6 months of treatment and should have adenoma size assessed by MRI once a year.[63] Whether or not GH levels should be monitored is not clear. In patients shown to have aggressive disease and significant residual tumour, pre-treatment with radiotherapy should be seriously considered before starting therapy with pegvisomant.

In patients with persistent biochemical or clinical disease activity it seems advisable to add a somatostatin analogue to pegvisomant. Alternatively, one might consider co-treatment of a somatostatin analogue and a dopamine agonist.

Finally, in those patients in whom adverse effects are still present after 6 months of treatment with a somatostatin analogue, if both the patient and the physician consider it a reason for discontinuation of this therapy, pegvisomant treatment should be commenced. In that case, the same safety guidelines should be considered, as stated earlier.

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