

# Therapeutic options in the management of acromegaly: focus on lanreotide Autogel®

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**Background:** In acromegaly, expert surgery is curative in only about 60% of patients. Postoperative radiation therapy is associated with a high incidence of hypopituitarism and its effect on growth hormone (GH) production is slow, so that adjuvant medical treatment becomes of importance in the management of many patients.

**Objective:** To delineate the role of lanreotide in the treatment of acromegaly.

**Methods:** Search of Medline, Embase, and Web of Science databases for clinical studies of lanreotide in acromegaly.

**Results:** Treatment with lanreotide slow release and lanreotide Autogel® normalized GH and insulin-like growth factor-I (IGF-I) concentrations in about 50% of patients. The efficacy of 120 mg lanreotide Autogel® on GH and IGF-I levels was comparable with that of 20 mg octreotide LAR. There were no differences in improvement of cardiac function, decrease in pancreatic  $\beta$ -cell function, or occurrence of side effects, including cholelithiasis, between octreotide LAR and lanreotide Autogel®. When postoperative treatment with somatostatin analogs does not result in normalization of serum IGF-I and GH levels after noncurative surgery, pegvisomant alone or in combination with somatostatin analogs can control these levels in a substantial number of patients.

**Keywords:** acromegaly, lanreotide, somatostatin analog, growth hormone, pegvisomant

## Introduction

Growth hormone (GH), a polypeptide consisting of 191 amino acids and which is secreted by the pituitary gland, has a multitude of effects. The most obvious effect is the stimulation of growth in prepubertal and pubertal children. In childhood, lack of this hormone leads to dwarfism and excessive secretion results in gigantism. Growth hormone has profound metabolic effects by stimulating protein anabolism and lipolysis. Other effects include stimulation of bone turnover, leading to a net increase in bone volume, muscle growth, insulin antagonism, renal sodium retention, and immuno modulation. Most of the effects of GH are indirectly mediated via insulin-like growth factor-I (IGF-I). IGF-I is a peptide synthesized and secreted as a result of GH-signaling, which acts locally in an autocrine or paracrine manner, or systematically as a hormone when secreted by the liver (Le Roith et al 2001). The liver secretes about 70% of the total circulating IGF-I in mice (Sjogren et al 1999).

Excessive secretion of GH leads to acromegaly, a disfiguring and debilitating condition causing severe co-morbidity and premature death (Wright et al 1970; Ezzat et al 1994; Melmed 2006; Ben-Shlomo and Melmed 2008).

The purpose of this review is to establish the role of lanreotide, particularly lanreotide Autogel®, in the management of acromegaly based on published data. It is appropriate, however, to outline first the clinical features of acromegaly and to discuss therapeutic approaches in its management.

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## Acromegaly

Acromegaly is a rare disease, caused by a GH-secreting adenoma and in even more seldom instances (about 1%) due to excessive GHRH secretion, usually by a carcinoid tumor of the lung or gastrointestinal tract (Biermasz et al 2007). The incidence of acromegaly is about 3–4 per 1 million per year and the prevalence is 60–70 per 1 million, without geographical or sex differences (Alexander et al 1980; Bengtsson et al 1988; Ritchie et al 1990; Mestron et al 2004). Clinical features of acromegaly include acral enlargement, prognatism, jaw malocclusion, arthropathy, carpal tunnel syndrome, hyperhidrosis, sleep apnea, and visceromegaly (Colao et al 2004; Melmed 2006). Acromegaly is also associated with increased cardiovascular morbidity and mortality. Active disease leads to a specific form of cardiomyopathy which involves myocardium, conduction system, and heart valves. Clinical manifestations include arrhythmias, valvular regurgitation, concentric left ventricular hypertrophy, and left ventricular systolic and diastolic dysfunction (Clayton 2003; Colao et al 2004; Pereira et al 2004). The incidence of hypertension and of decreased glucose tolerance is also increased. This is also true for the incidence of colon polyps and colon carcinoma (Orme et al 1998; Renehan and Shalet 2002). It is controversial, however, whether the relative risk of cancer is increased in patients with acromegaly compared with that of the general population (Jenkins and Besser 2001; Melmed 2001; Loeper and Ezzat 2008).

Local tumoral symptoms include chronic headache, visual field defects, and rarely cranial nerve palsies. Hypopituitarism is mostly associated with large tumors with a generally low incidence in patients with acromegaly varying from 3% to 10% (Greenman et al 1995).

The increased standardized mortality rate (SMR) decreased from 3-fold in older series to 1.3-fold in series with predominantly primary transsphenoidal surgery (Swaering et al 1998; Holdaway et al 2004; Kauppinen et al 2005; Holdaway 2007; Dekkers et al 2008). Reported risk factors include diabetes mellitus, cardiomyopathy, sleep apnea, and cerebrovascular events and in some, but not all, studies also pituitary irradiation (Ayuk et al 2004; Biermasz et al 2004a; Kauppinen et al 2005). The decrease in mortality observed in acromegaly is likely to be due to the introduction of effective therapies such as transsphenoidal surgery in the 1970s and to postoperative radiotherapy, leading to normalization of GH and IGF-I concentrations in a substantial number of patients. The effective treatment of systemic co-morbidities also plays a role in the observed decrease in mortality. Only few patients using adjuvant somatostatin analogs are included in mortality

series and it is of note that at present no mortality data exist for primary medical treatment including pegvisomant treatment. Most studies have suggested that a lower GH, for example below 2.5  $\mu\text{g/L}$ , is associated with improved and even normal survival. In some but not all studies normal IGF-I was also associated with improved mortality (Ayuk et al 2004; Biermasz et al 2004a; Holdaway et al 2004; Kauppinen et al 2005). Discrepancies between studies may be explained by a single GH or IGF-I measurement being used in most studies, which is hardly representative for disease status in the entire follow-up period; by the unavailability of IGF-I in a substantial number of patients; and by GH and IGF-I assay differences. In addition, individual mortality studies consist of relatively small numbers of patients with large confidence intervals including 1.0, limiting statistical power.

In acromegaly detailed studies of spontaneous GH secretion have demonstrated increased pulsatility (increased pulse frequency), amplified burst mass, and increased basal secretion, associated with decreased regularity (Barkan et al 1989; Ho et al 1994; van den Berg et al 1994). Biochemical criteria of active disease and remission are the (mean) GH level, glucose-suppressed GH concentration, and the IGF-I level (Giustina et al 2000). GH assays differ in specificity, sensitivity, and GH standard, and therefore individual clinical endocrine laboratories should establish normal ranges of gender- and age-related GH and IGF-I values and ideally corrected for fat mass or a fat mass-derived parameter (Gullu et al 2004; Bidlingmaier and Strasburger 2007). Circulating IGF-I reflects GH secretion rate and serum concentrations of IGF-I are elevated in all patients with active disease (Melmed 2006). IGF-I concentrations decrease with advancing age. In addition, gender, sex hormone status, the use of oral estrogens, thyroxin, and body composition can all influence IGF-I concentrations (Clemmons 2007).

## Treatment of acromegaly

As discussed above, epidemiological studies have clearly demonstrated that controlling GH and IGF-I secretion is the most significant determinant of restoring survival in patients with acromegaly. The main goal of treatment of acromegaly is therefore to achieve GH levels of less than 1  $\mu\text{g/L}$  after a glucose load, to normalize age- and gender-matched IGF-I levels, to ablate or reduce tumor mass and prevent its recurrence, and to alleviate significant co-morbidities, especially cardiovascular, pulmonary, and metabolic disturbances (Melmed et al 2002). The currently available treatment modalities for acromegaly are selective transsphenoidal adenomectomy, radiotherapy, medical treatment, or combinations thereof.

## Transsphenoidal surgery

This oldest treatment modality was developed a century ago by the Austrian neurosurgeon Schloffer (Schloffer 1907). It is generally performed via the transnasal, transsphenoidal route and is associated with low morbidity and mortality. In recent years most neurosurgeons have adopted the endoscope in lieu of the surgical microscope, which has obvious advantages for the patient and also leads to better visualization of the operating field. Other variants of surgical techniques are neuronavigating and real-time intraoperative MRI scanning, aimed at visualization of tiny tumor remnants after resection of the adenoma (Fahlbusch et al 2005; Thomale et al 2005). GH secretion pattern is restored when the adenoma is completely removed (van den Berg et al 1998). Surgical cure is highest in patients with a microadenoma (diameter less than 10 mm) varying from 80% to more than 90% in the hands of experienced neurosurgeons. However, complete tumor removal becomes more difficult with increasing size of the tumor and expansion into the neighboring delicate structures, and the cure rate of large macroadenoma drops to only 20%–40% of cases (Freda et al 1998; Biermasz et al 2000a; Kaltsas et al 2001; Kreutzer et al 2001; Shimon et al 2001; Beauregard et al 2003; De et al 2003; Nomikos et al 2005; Lüdecke and Abe 2006). The obvious advantage of successful surgery is the rapid normalization of GH secretion and decrease in IGF-I levels, while the complication of (partial) hypopituitarism is generally below 10% (Nomikos et al 2005; Lüdecke and Abe 2006). Second surgical procedures are generally safe but less successful than primary surgery (Long et al 1996). The experience of the neurosurgeon is critical for a high cure rate (Ahmed et al 1999; Bates et al 2008).

## Radiotherapy

Conventional radiotherapy is administered by a linear accelerator (4–8 MeV) with a total dose of 40–45 Gy, fractionated in at least 20 sessions. A rotational field, 2 opposing fields, or a 3-field technique are used. A mean GH decrease of about 50% is observed in the first 2 years after irradiation and after 5 years a 75% decline is reported (Biermasz et al 2000b; Wass et al 2003). Whether the GH level normalizes post irradiation mainly depends on pre-irradiation serum GH concentration and the time interval between radiotherapy and the measurement of GH and IGF-I levels. Post-irradiation remission rates are, however, largely affected by the extent of surgical debulking prior to radiotherapy. Other than the slow onset of GH control another drawback is the increasing incidence of hypopituitarism varying from 50%–85% after a follow-up of 10 years or longer (Minniti et al 2005; Biermasz et al 2006).

Barkan and colleagues were the first to question the efficacy of radiotherapy in normalizing serum IGF-I concentrations, with many studies addressing the effects of conventional pituitary irradiation on IGF-I and strict GH criteria being reported thereafter (Barkan et al 1997). A few reports supported an apparent lack of efficacy of pituitary irradiation (Thalassinos et al 1998; Cozzi et al 2001), whereas others reported normalization of IGF-I in 44%–79% of patients after 5–15 years of follow-up (Ciccarelli et al 1993; Barrande et al 2000; Powell et al 2000; Epaminonda et al 2001; Minniti et al 2005).

Another radiation technique is radiosurgery, which is the precise, stereotactic delivery of a single high radiation dose to a defined target with a steep dose gradient at the tumor margin (Mahmoud Ahmed et al 2001; Castinetti et al 2005; Roberts et al 2007). This form of radiotherapy is performed using a gamma knife with up to 200 <sup>60</sup>Co sources, a Linac-based system, or proton beams (Marcou and Plowman 2000; Brada et al 2004; Sheehan et al 2005). The perceived advantage of this form of irradiation is that only one session is required. There is otherwise no convincing evidence as yet that radiosurgery is superior to conventional irradiation in terms of GH control, time needed to reach clinically acceptable GH levels, and incidence of hypopituitarism (Landolt et al 1998; Attanasio et al 2003a; Biermasz et al 2006).

Disadvantages of pituitary irradiation other than the development of hypopituitarism include decreased quality of life (QoL), the development of secondary tumors, cerebrovascular disease, and increased mortality. In one cross-sectional study, decreased health-related QoL was described in acromegalic patients in long-term remission (Biermasz et al 2004b). These data were confirmed by another QoL analysis of treated acromegalic patients (Rowles et al 2005). A significant predictor of poor QoL was radiotherapy, but the pathophysiologic mechanism remains unclear. Increased mortality due to cerebrovascular disease was observed in two of the studies (Ayuk et al 2004; Kauppinen et al 2005) but not in the other three (Bates et al 1993; Ahmed et al 1999; Biermasz et al 2004a). The effect of radiotherapy on mortality is thus as yet to be established. The likelihood of secondary tumor formation after pituitary irradiation is very low (Brada et al 1992).

## Medical treatment

The three most important drugs used for medical treatment of acromegaly are dopamine agonists, somatostatin analogs, and GH-receptor modulating chemicals.

### Dopamine agonists

Bromocriptine, a dopamine agonist, effectively reduces GH secretion in only a minority of GH-secreting adenoma (Jaffe and Barkan 1992). Cabergoline, a more potent dopamine agonist with prolonged duration of action, was reported to normalize GH in 35% and IGF-I in 44% of 46 patients with a purely GH-secreting adenoma when given at a dose of 1–1.75 mg/week (Abs et al 1998). The efficacy of cabergoline was somewhat better in tumors co-secreting prolactin. Quinagolide, another dopamine agonist, was reported to normalize IGF-I in 28% of patients (Freda 2003). Most endocrinologists use long-acting dopamine agonists as adjunct therapy in patients who fail to normalize GH secretion with octreotide monotherapy. The combination therapy normalizes serum IGF-I concentrations in 30%–40% of patients, irrespective of the prolactin concentration (Cozzi et al 2004). Side effects of cabergoline are rare although there has been recent concern about cardiac valve hypertrophy, as observed in patients with Parkinson's disease. Whereas the dose in Parkinson's disease is generally much higher than that used for endocrine indications (Schade et al 2007), patients with acromegaly generally require long-term medical treatment for GH control. The use of dopaminergic drugs other than cabergoline is probably safer in acromegaly.

### Somatostatin analogs

Somatostatin was isolated in 1973 from the hypothalamus and subsequently synthesized (Brazeau et al 1973). The hormone is processed from a large pre-prohormone into 2 cyclic peptides, consisting of 14 or 28 amino acids. The short form, SS14, is predominantly present in the brain, whereas SS28 is widely distributed in peripheral organs. Somatostatin acts as neuromodulator and neurotransmitter in the brain and as a neurohormone in the regulation of GH and thyroid-stimulating hormone secretion. In addition, somatostatin inhibits tumoral adrenocorticotrophic hormone secretion in Cushing's disease (van der Hoek et al 2004). Somatostatin acts as neurotransmitter in the extensive myo-enteric plexus, and as hormone in a paracrine and autocrine fashion. Via specific receptors, somatostatin exerts many inhibitory effects on gut and pancreatic hormones, including gastrin, insulin, glucagon, vasoactive intestinal peptide, motilin, and gastric inhibitory polypeptide. Other effects of somatostatin include inhibition of gastric emptying, pancreatic enzymes and bicarbonate secretion, gastrointestinal blood flow and bile flow (Brazeau et al 1973; Reichlin 1983; Patel 1999). Somatostatin acts via a G-protein-coupled receptor, of which 5 subtypes have been cloned and characterized (Lamberts et al 1996).

After binding of somatostatin to its receptor, the activities of adenylyl cyclase and of calcium channels are inhibited, whereas phosphotyrosine phosphatase activity and mitogen-activated protein kinases activity are stimulated. The first two processes are involved in the inhibition of secretory processes, and the latter two may play a role in cell proliferation, eg, activation of the SST3 receptor may induce apoptosis (Danilla et al 2001; Bevan 2005). Analogs of somatostatin differ in binding properties to different receptor subtypes (Lamberts et al 1996). Many benign and malign tumors express one or more somatostatin receptors. Receptor distribution and density and homogeneity of receptor expression within the tumor determine whether a particular analog can be effectively used therapeutically (Krantic et al 2004; Olias et al 2004).

GH-secreting pituitary adenomas express predominantly SST2 and SST5 receptors. The current clinically used analogs, octreotide and lanreotide, inhibit GH secretion via the somatostatin receptor subtypes 2 and 5 (Hoffland and Lamberts 2003). The plasma half-life of these analogs is about 20 times longer than that of native somatostatin, which is less than 3 minutes (Lamberts et al 1996). Although the most important effect of somatostatin analogs is the inhibition of GH secretion by the adenoma leading to a subsequent decrease in circulating liver-derived IGF-I, part of the peripheral effects of these analogs is caused by the direct inhibition of IGF-I gene transcription after binding to the somatostatin receptor (Serri et al 1992; Murray et al 2004). The magnitude of this latter effect in various organs is not exactly known.

### GH receptor antagonists

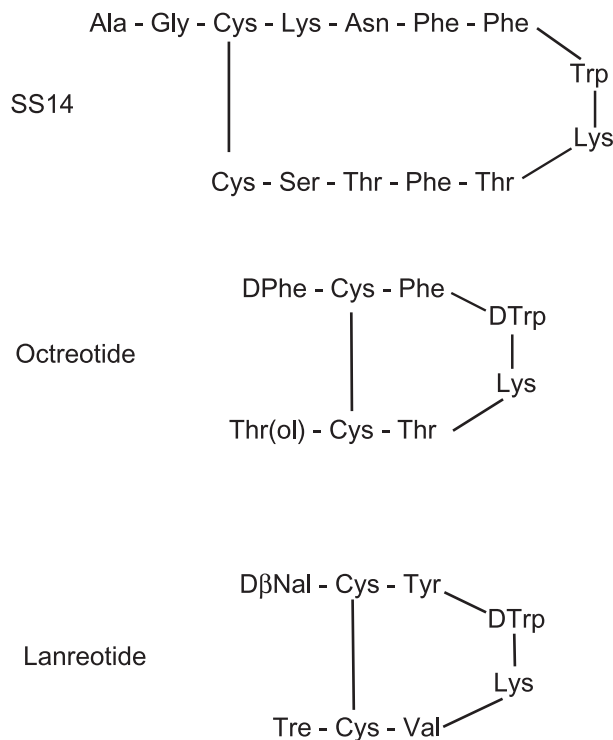
Pegvisomant is an engineered GH analog that antagonizes GH at the receptor site, and thus prevents endogenous GH activation of its receptor and subsequent downstream signaling. In short-term studies, the lowest dose (10 mg/day) normalized IGF-I in 38% of the patients and 20 mg normalized IGF-I in 82% of patients (Trainer et al 2000; van der Lely et al 2001). In a minority of patients (2 out of 112 and 7 out of 229 patients, respectively) adenoma size increased during a relatively short treatment period (van der Lely et al 2001; Schreiber et al 2007). Careful documentation of tumor size before starting pegvisomant treatment is therefore compulsory and long-term monitoring is advisable. A small number of patients (2 out of 167 cases) developed abnormalities in liver function tests, necessitating withdrawal of the drug, although increased liver enzyme levels, ie, more than 3 times the upper level of normal, was observed in 5.5% of 229 patients, normalizing spontaneously in 3.1%

on continuing treatment (van der Lely et al 2001; Schreiber et al 2007). About 40% of patients develop minor abnormalities in liver function tests on combined treatment with somatostatin analogs, which do not require stopping of the drug and which usually resolve spontaneously (Feenstra et al 2005).

## Pharmacokinetics of lanreotide

The first pharmaceutical available form of lanreotide (BIM 23014) was relatively short-acting, requiring multiple dosing, 3 times a day, or subcutaneous infusion. This was nevertheless a major advance in the treatment of many patients who had already undergone unsuccessful surgery and pituitary irradiation and for whom there were no other treatment options (Figure 1). In healthy subjects, maximal serum concentrations of lanreotide were reached after 30 min and the serum half-life was 90 min, 30 times greater than that of native somatostatin (Kuhn et al 1994; Antonijoan et al 2004; Table 1). Subsequently, a long-acting form of lanreotide was developed by incorporating the drug into polyactide – polyglycolide microspheres, so that the half-life was considerably prolonged, and the injection interval could be extended to 7–14 days (Heron et al 1993). The lanreotide release pattern from the long-acting form is biphasic, ie, an early release during 2 days from the drug adsorbed onto the surface of the

microspheres, followed by sustained release for about 1 week, starting at day 4, as a result of enzymatic breakdown of the microspheres, followed again by an exponential decrease in drug release. It was subsequently discovered that lanreotide had the unique property of self aggregation under favorable conditions, leading to a stable structure of highly organized nanotubules (Valery et al 2003, 2008). This formulation of the drug was named lanreotide Autogel® and has a long half-life after subcutaneous injection determined by pseudo-first order kinetics. Maximal serum concentrations are reached after 1–2 days (see Table 1) in healthy subjects and the serum half-life amounts to 25.5 days (Antonijoan et al 2004; Astruc et al 2005). In acromegalic patients maximal values are reached after 3.8–7.7 days under steady state conditions, depending on the dose administered (Table 2). Simulated steady state pharmacokinetic profiles of long-acting octreotide and lanreotide Autogel® differ significantly (Astruc et al 2005; Bronstein et al 2005). During long-acting octreotide treatment, serum concentrations of the drug are more or less stable, whereas the characteristic first-order kinetics of lanreotide Autogel® is superimposed on levels just before the next administration (see Figure 2; Astruc et al 2005). The pharmacokinetic differences therefore indicate that octreotide LAR can be better tailored to therapeutic levels, whereas serum levels of lanreotide must be (too) high for part of the interval between injections in order to be effective in the period before the next administration. The possible clinical consequence(s) of these different pharmacokinetic profiles can be resolved only in long-term studies in which lanreotide Autogel® is compared with octreotide or drugs with a similar pharmacokinetic profile.



**Figure 1** Amino acid structure of somatostatin-14, octreotide, and lanreotide.

## Efficacy of lanreotide

The first studies with lanreotide were performed using lanreotide Slow Release (lanreotide SR). The drug was first available in vials containing 30 mg, to be injected at 2-weekly intervals. The interval was shortened, however, to 7–10 days when GH was insufficiently suppressed. The drug later also became available in vials containing 60 mg of lanreotide so that the injection interval could be extended to 4 weeks, similar to that of the long established octreotide LAR. Studies using lanreotide SR 30 mg and lanreotide SR 60 mg are summarized in Table 3. Most patients had undergone pituitary surgery and many were irradiated, either as primary treatment (a minority) or as adjuvant treatment after noncurative surgery. In addition, in almost all studies patients had been treated with octreotide. Normal mean GH concentration, as defined by the authors (generally below

**Table 1** Pharmacokinetic analysis of a single subcutaneous dose of short-acting lanreotide and lanreotide Autogel® in healthy subjects

	Short-acting lanreotide <sup>a</sup> n = 24	lanreotide Autogel <sup>a</sup> n = 24	lanreotide Autogel <sup>b</sup> n = 10	lanreotide Autogel <sup>b</sup> n = 10
Dose	7 µg/kg	60 mg	90 mg	120 mg
C <sub>max</sub>	7.98 ng/mL	5.71 ng/mL	6.7 ng/mL	
T <sub>max</sub>	0.43 h	0.38 day	2.4 day	1.1 day
Half-life	1.74 h	22 days	25.5 day	
AUC	16.51 ng.mL <sup>-1</sup> .h	79.48 ng.mL <sup>-1</sup> .day	116 ng.mL <sup>-1</sup> .day	133 ng.mL <sup>-1</sup> .day
MRT	1.95 h	31.97 days		

<sup>a</sup>Antonijooan et al (2004); <sup>b</sup>Astruc et al (2005).

**Abbreviations:** AUC, area under the curve; MRT, mean residence time.

2.5 µg/L) was achieved in 23%–93% of the cases treated with lanreotide SR 30 mg, and in 25%–65% of the cases treated with lanreotide 60 mg. Normal values of IGF-I were obtained in 23%–68% of patients on lanreotide SR 30 mg, and 35%–62% of these on lanreotide SR 60 mg. The weighted means of normalization of GH and of IGF-I were 54% and 49%, respectively, during treatment with 30 mg lanreotide, whereas during treatment with lanreotide SR 60 mg these values were 60% and 58%.

Comparative studies of efficacy between octreotide and lanreotide are summarized in Table 4. Short-acting octreotide, mostly given 3 times a day, had a similar GH-suppressive effect as lanreotide SR. Normal GH was obtained in 52% and 49% of a total of 218 patients, but normalized IGF-I was more frequently found in patients treated with lanreotide SR 30 mg/10–14 days, ie, 49% versus 64%. The efficacy of octreotide LAR was slightly higher than that of lanreotide SR: normalized GH and IGF-I were obtained in 64% and 62% of 155 patients treated with octreotide LAR versus 52% and 50%, respectively, in the same patients during treatment with lanreotide SR. A limitation of all these studies, with one exception, is that they were not randomized. The overall better efficacy of octreotide LAR compared with lanreotide SR agrees with findings from a recent meta-analysis (Freda et al 2005).

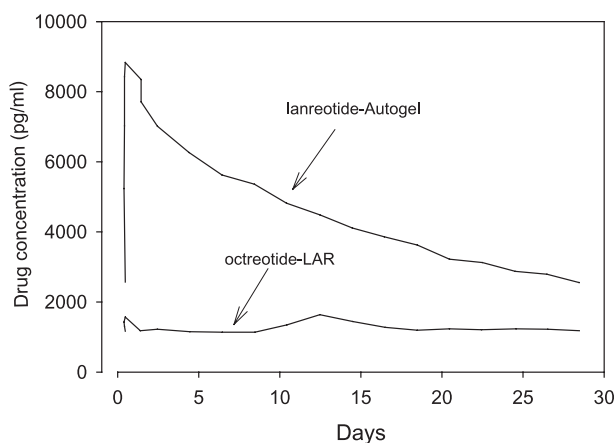
**Table 2** Pharmacokinetics of lanreotide Autogel® during steady state conditions in patients with acromegaly

Dose	60 mg	90 mg	120 mg
T <sub>max</sub> (days)	85	84	85
C <sub>mean</sub> (ng/mL)	2.46	3.04	4.52
C <sub>min</sub> (ng/mL)	1.82	2.51	3.76
C <sub>max</sub> (ng/mL)	3.82	5.69	7.69
AUC (ng.mL <sup>-1</sup> .day)	68.8	85.1	127

From data of Bronstein et al (2005).

**Abbreviation:** AUC, area under the curve.

Lanreotide Autogel® was introduced about 8 years ago, and the first report in the English literature was published in 2002. Clinical efficacy studies are summarized in Table 5. Most of the patients who took part in these studies had undergone pituitary surgery, often with adjuvant irradiation, and almost all patients were on octreotide or lanreotide SR treatment, while a minority also used dopaminergic drugs. The results of these studies should therefore be considered critically, as a selection bias cannot be excluded. Normal GH, defined as a concentration below 2.5 µg/L in fasting single blood samples or as the mean of serial samples was observed in 38%–80% of cases and normal age-related IGF-I was recorded in 39%–80% of patients on lanreotide Autogel®. In these studies the weighted mean for GH normalization was 58% and for IGF-I 48% in a population of 370 patients. The results mentioned above refer to measurements at the end of the study when dose titration of lanreotide Autogel® was fully effective. Indeed, most of the patients ended receiving the highest dose of 120 mg. These results do not differ from



**Figure 2** Pharmacokinetic profiles of lanreotide Autogel® (90 mg) and octreotide-LAR (20 mg) at steady state. The lines represent mean values of 10 simulated profiles. From data of Astruc et al (2005).

**Table 3** Efficacy of lanreotide slow release (SR) on serum GH and IGF-I concentrations in acromegaly

Reference	Patient no	Previous surgery and/or radiotherapy	Previous medication (number)	Used medication	Duration (months)	GH normal	IGF normal	Comments
Heron 1993	14	14	none	Lanreotide SR 30 mg/14 d	6	93%	64%	IGF-I < 350 ng/mL, GH < 5 µg/L
Johnson 1994	8	5	none	Lanreotide SR 30 mg/14 d	6	50%	38%	No SDS for IGF-I, GH < 10 mU/L
Marek 1994	13	13	none	Lanreotide SR 30 mg/14 d	9–19	23	23%	IGF-I < 270 µg/L, GH < 5 µg/L
aI-Maskari 1996	10	10	octreotide (7)	Lanreotide SR 30 mg/10–14 d	6	60%	50%	No SDS for IGF-I, GH < 5 mU/L
Caron 1997	22	7	octreotide (21)	Lanreotide SR 30 mg/10–14 d	6–36	27.2%	64%	IGF < 300 ng/mL for all subjects
Giusti 1997	57		octreotide SR (37)	Lanreotide SR 30 mg/10–14 d	6	54%	35%	Normal IGF < mean + 3SD; normal GH < 5 µg/L
Morange 1994	19	13	octreotide (14)	Lanreotide SR 30 mg/10–14 d	6	68%	68%	IGF-I not age-adjusted
Suliman 1999	30	21	octreotide (7)	Lanreotide SR 30 mg/10–14 d	12	78%	35%	IGF-I not age-adjusted
Colaio 1999	45	25	octreotide (45)	Lanreotide SR 30 mg/10–14 d	6	58%	58%	Age-adjusted IGF-I
Baldelli 2000	118	95	octreotide (95)	Lanreotide SR 30 mg/10–14 d	24	61%	52%	Age-adjusted IGF-I
Verhelst 2000	66	37	octreotide (55)	Lanreotide SR 30 mg/7–14 d	12	45%	44%	Age-adjusted IGF-I
Chanson 2000b	58	58	octreotide (38)	Lanreotide SR 30 mg/10–4 d	12	41%	41%	Selected from 116 patients
Cannavo 2000	18	10	octreotide (16)	Lanreotide SR 30 mg/10–30 d	6	50%	44%	IGF-I not age-adjusted
Cozzi 2000	10	none	none	Lanreotide 60 mg/28–21 d	6	25%	62%	IGF-I not age-adjusted
Ambrosio 2002	20	13	lanreotide SR 30 mg/octreotide (15)	Lanreotide 60 mg/28–21 d	8	65%	35%	Age-adjusted IGF-I
Attanasio 2003b	92	62	octreotide or lanreotide SR (40)	Lanreotide 60 mg/28/21/14 d	24	63%	65%	Age-adjusted IGF-I

**Table 4** Comparison of efficacy of octreotide versus lanreotide SR in acromegaly

Reference	Number of patients	Octreotide		Lanreotide	
		GH normalized	IGF-I normalized	GH normalized	IGF-I normalized
Morange 1994	19	16/19	16/19	8/19	13/19
Caron 1997	21	12/21	17/21	6/22	14/22
Colao 1999	45	23/45	23/45	26/45	26/45
Razzore 1999	38	18/38	19/38	9/38	16/38
Baldelli 2000	95	45/95	32/95	58/95	72/95
Kendall-Taylor 2000	5	4/5	5/5	4/5	5/5
Turner 1999	10	8/10	7/10	7/9	5/9
Cozzi 1999	12	4/10	5/10	1/10	4/10
Chanson 2000b	125	68%	65%	54%	48%
Amato 2002 <sup>§</sup>	20	50%	50%	58%	67%

<sup>§</sup>Randomized study

**Table 5** Clinical studies with lanreotide Autogel® in acromegaly

Reference	Study design	Patient no. ITT/PPP	Previous treatment PS/RT/MT	Dosing lanreotide Autogel	Duration (months)	Normal GH (< 2.5 µg/L)	Normal age-adjusted IGF-I	Previous medication
Caron 2002	open label MC	144/107	83/49/107	60/90/120 mg	3	56%	48%	LSR 30 mg/7-14 d
Alexopoulou 2004	open label MC	25/25	13/5/25	60/90/120 mg	6	48%	52%	oLAR 20-40 mg/4 w
Ashwell 2004	open label MC	12/10	7/5/10	60/90/120 mg	7	80%	80%	oLAR 20 mg/4 w
Caron 2004	extension study	131/130	99/57/131	60/90/120 mg	12	68%	50%	Lan-Autogel
Gutt 2005	open label	11	10/0/11	60/90/120 mg	16	?	54%	LSR 30 mg/7-14 d
Caron 2006	extension study	14/14	9/5/14	60/90/120 mg	36	77%	54%	LSR 30 mg/10-14 d
Lucas 2006	open label MC	99/93	76/53/99	120 mg/4-8 w	3	54%	55%	LSR 30 mg/7-14 d
Ronchi 2007	open label MC	23/21	2/0/23	60/90/120 mg	9	56%	39%	oLAR 10-30 mg/4 w
Andries 2008	randomized cross-over	12/10	7/3/11	Fixed dose 60/90/120 mg	12	42% <sup>a</sup>	50%	oLAR 10-30 mg/4 w
Chanson 2008	open label MC	63/57	37/12/49	Fixed phase and dose titration	12	38%	43%	oLAR, lanreotide SR, lanreotide Autogel, washout

<sup>a</sup>normal GH concentration <0.38 µg/L.

**Abbreviations:** ITT, intention-to-treat; PPP, patients per protocol; PS, pituitary surgery; RT, radiotherapy; MT, previous medical treatment; LRS, lanreotide slow release; oLAR, octreotide LAR; MC, multicenter.



data obtained in patients on lanreotide SR (see above). Part of these studies compared the efficacy of octreotide LAR and lanreotide Autogel®. A drawback of these studies is that with the exception of one study none were randomized (Andries et al 2008). An open-label, uncontrolled, single-group assignment study on the effects of lanreotide Autogel® in 27 previously untreated patients with acromegaly was recently completed (ClinicalTrials.gov NCT00627796). Although the study is rather small it will contribute further data on IGF-I control and tumor reduction.

In a 3-month study in 107 patients, the normalization rate for GH was 48% during lanreotide SR and 56% during lanreotide Autogel® therapy, whereas a normal IGF-I was obtained in respectively 45% and 48% of cases (Caron et al 2002). In an extension phase of this study to 12 months, normalized GH frequency increased from 49% to 68% in 130 patients; these figures were 44% and 50% for IGF-I (Caron et al 2004). Fourteen patients of these studies were treated for 3 years with lanreotide Autogel®. In these patients the frequency of normal GH increased from 36% to 77% and that for IGF-I from 36% to 54% (Caron et al 2006). Finally, the Spanish multicenter study extended the Autogel® injection interval to 8 weeks in patients who were controlled by 2-weekly injections with lanreotide SR. The overall GH control increased from 46% to 54% (Lucas et al 2006). The studies comparing the efficacy between octreotide LAR and lanreotide are shown in Table 6. Only the small study by Andries was properly designed, and showed equal efficacies of both drugs in terms of normalization of GH. Nevertheless, this study demonstrated a better GH-suppressive effect of octreotide on absolute GH concentrations than lanreotide. In contrast, the suppressive effect on IGF-I was similar. There was no difference in GH suppressive effect in a small study in 7 patients in whom the 24 h GH secretion was precisely measured with a 10 min blood sampling protocol. (Van Thiel et al 2004). From the data presented above and despite limitations in design, it would appear that lanreotide Autogel® and octreotide LAR

are equipotent in normalizing GH and IGF-I concentrations. Although patients require generally the highest lanreotide dose, most patients on octreotide LAR had safe GH and normal IGF-I levels on the 20 mg dose. For the practicing endocrinologist the message is that patients on octreotide LAR 20–30 mg need 120 mg lanreotide Autogel® and somatostatin-sensitive patients on octreotide LAR 10 mg require mostly 90 mg of the Autogel® formulation. Lanreotide Autogel® is registered under the trade name Somatuline Autogel® in the majority of countries, as Somatuline Depot Injection® in the US, and as Ipstyl Autogel® in a few European countries.

## Side effects

The most frequent side effects of lanreotide are diarrhea, abdominal pain, and nausea. These symptoms start mostly shortly after an injection, decrease subsequently, and tend to decrease in severity on continuing treatment. Table 7 lists the side effects mentioned in the clinical studies with the 2 long-acting formulations of lanreotide. For the SR formulation the gastrointestinal side effects were observed in 48% of the patients and for the Autogel® formulation in 52%. The most serious complication of somatostatin analogs is cholelithiasis. The prevalence of somatostatin analog-induced gallstones varies geographically and may be influenced by dietary, environmental, and racial factors. The formation of gallstones involves the inhibition of gallbladder emptying and intestinal motility, inhibition of the secretion of prokinetic peptides, including cholecystokinin, and increased intestinal and biliary production of deoxycholic acid, all of which promote the nucleation of cholesterol crystals and their aggregation into stones (Dowling et al 1992). We analyzed the occurrence of new cholelithiasis in patients who were already on somatostatin analog treatment, a condition thus not quite comparable to drug-naïve patients in terms of risk of developing gallstones. The incidence of new gallstones was 6% for lanreotide SR and 8.7% for lanreotide Autogel®. These figures are smaller than generally cited in literature,

**Table 6** Efficacy of lanreotide Autogel® compared with octreotide LAR and lanreotide SR in acromegaly

Reference	Duration (months)	Patient no ITT/PPP	Octreotide LAR dose	Lanreotide Autogel dose	Normal GH oLAR	Normal GH lanreotide Autogel	Normal IGF-I oLAR	Normal IGF-I lanreotide Autogel
Alexopoulou 2004	6	25/25	20–40 mg/4 w	60/90/120 mg	64%	48%	52%	52%
Ronchi 2007	9	23/21	10–30 mg/4 w	60/90/120 mg	40%	56%	35%	39%
Andries 2008	12	12/10	10–30 mg/4 w	Fixed dose 60/90/120 mg	50%	50% <sup>a</sup>	50%	60%

<sup>a</sup>normal GH concentration <0.38 µg/L.

**Abbreviations:** ITT, intention-to-treat; PPP, patients per protocol; oLAR, octreotide LAR.

**Table 7** Side effects during treatment with lanreotide SR and lanreotide Autogel® in acromegaly

Author	Number of patients	Number of naive patients	Current treatment	GI side effects	New cholelithiasis	Fasting glucose	Tumor size decrease
Heron 1993	14	0	LSR 30 mg	9	2	nc	
Morange 1994	19	0	LSR 30 mg	3	2	nc	
Johnson 1994	8	3	LSR 30 mg	5	1	nd	nd
Marek 1994	13	0	LSR 30 mg	13	1	nc	5/13 (>20%)
Giusti 1996	57	0	LSR 30 mg	22	2	nc	
al-Maskiri 1996	10	0	LSR 30 mg	10	1	nc	
Caron 1997	22	0	LSR 30 mg	13	4	nc	
Suliman 1999	30	7	LSR 30 mg	26	2	nc	1/7
Colao 1999	45	0	LSR 30 mg	12	1	nm	
Chanson 2000a	58	0	LSR 30 mg	40	6	nc	
Baldelli 2000	118	23 <sup>a</sup>	LSR 30 mg	64	4	nm.	5/23 (>20%)
Cozzi 2000	21	8	LSR 60 mg	nd	0	nc	5/13
Cannavo 2000	22	0	LSR 30 mg	few	2	nm.	
Verhelst 2000	66	3	LSR 30 mg	41	2	nc	
Ambrosio 2002	20	0	LSR 60 mg	10	0	nc	0/4
Attanasio 2003b	92	22	LSR 60 mg	8	10	nc	11/22
Caron 2004	130	0	LAUT	58	12	nd	
Ashwell 2004	12	0	LAUT	0	nd	nd	
Alexopoulou 2004	25	0	LAUT	8	0	nc	
Ronchi 2007	23	0	LAUT	nd	1	nc	
Chanson 2008	63	nd	LAUT	53	8	increase in 4	

Decrease of tumor size is given only for patients who had no previous radiotherapy or somatostatin analog treatment. <sup>a</sup>Six patients had been treated with bromocriptin.

**Abbreviations:** nd, no data available; nc, no significant change of glucose concentrations; nm, not mentioned; LSR, lanreotide slow release; LAUT, lanreotide Autogel.

but many patients had cholelithiasis caused by previous treatment.

Other side effects were local pain after injection and rarely (less than 1%) the development of nodules at the injection site. However, local infiltration signs did not decrease the efficacy of the drug. Other uncommon side effects included sinus bradycardia, asthenia, headache, pruritus, decreased libido, increased serum bilirubin, fatigue, constipation, and hair loss.

## Influence of lanreotide Autogel® on clinical manifestations

Some studies have investigated specific aspects of lanreotide action in acromegaly. These include detailed studies on glucose and insulin metabolism, effects on cardiac function, tumor growth, quality of life, and predictors of clinical response. These reports are briefly summarized below.

### Insulin and glucose homeostasis

GH is important in regulating glucose tolerance and insulin sensitivity. GH counteracts the effects of insulin by inhibiting the phosphorylation of the insulin receptor. Moreover, GH also inhibits the phosphorylation of one of the proximate

molecules of the insulin signaling cascade, insulin receptor substrate-1 in response to insulin (Kuhn et al 1992). In acromegaly, several studies have shown that increased GH induces insulin resistance (Kasayama et al 2000). However, GH also potentiates insulin release which is reflected in the high prevalence of high insulin levels both at rest and after glucose challenge (Cerasi and Luft 1964). Indeed, many untreated patients exhibit decreased glucose tolerance and more detailed studies have shown reduced insulin-stimulated glucose disposal in muscle and impaired non-oxidative glucose metabolism (Sonksen et al 1967; Wass et al 1980; Hansen et al 1986; Foss et al 1991; Koop et al 1994). Effects of somatostatin analogs on glucose homeostasis are the resultant of delayed intestinal absorption of carbohydrates, inhibition of insulin release and increased insulin sensitivity via diminished GH secretion. Results from studies with lanreotide do not differ essentially from earlier data obtained with octreotide. The acute effects of subcutaneously infused lanreotide were studied in healthy subjects. Oral glucose tolerance worsened during the first day of administration, but was restored on day 7 while drug administration continued (Kuhn et al 1992). In a study in 27 patients the homeostasis

model assessment (HOMA) index improved, but not the quantitative insulin check index (QUICKI) index (Ronchi et al 2003). In a cross-sectional study with 51 acromegalic patients of whom 18 were on lanreotide Autogel® the pancreatic  $\beta$ -cell function deteriorated but insulin resistance remained unchanged (Steffin et al 2006). The most precise study used the euglycemic hyperinsulinemic clamp. Twenty-four patients were studied at baseline and after 6 months treatment with either octreotide LAR or with lanreotide SR. Hemoglobin A1c (HbA1c) increased significantly. In patients with a normal glucose tolerance at baseline the glucose concentration at 120 min increased, together with decreased and delayed insulin response. Insulin sensitivity increased in all 12 clamped patients. The investigators could not demonstrate differences between octreotide and lanreotide, ie, the effects on GH, IGF-I, and insulin were all similar (Baldelli et al 2003). The effects of other pharmacologic therapies currently used for the treatment of acromegaly on glucose metabolism and insulin resistance were recently reviewed (Pereira et al 2005). In most studies, not specifically focused on insulin and glucose metabolism, fasting glucose concentrations and/or HbA1c levels did not change significantly when the GH-suppressive medication was changed to lanreotide or when the period of lanreotide administration was compared with the period without GH-suppressive medication.

### Cardiac effects

Acromegaly is associated with increased cardiac morbidity and mortality. Recognized cardiac manifestations include chronic cardiac failure due to systolic dysfunction (cardiomyopathy) or isolated diastolic dysfunction (Colao et al 2004; Pereira et al 2004). In addition, our group documented the increased prevalence of regurgitant valvular heart disease in acromegaly (Pereira et al 2004). An important question is whether effective GH-suppressive medication can improve cardiac function. One of the first studies reported on 13 patients treated with lanreotide. In this study there was a parallel decrease in GH and IGF-I and in left ventricular mass index; these data were confirmed in another study (Baldelli et al 1999; Hradec et al 1999). Octreotide was used in most studies on cardiac function, because this drug was the earliest available for clinical studies (Maison et al 2007). These studies indicate that effective GH-suppressive medication improves morphological and functional hemodynamic parameters, although medical therapy does not normalize all parameters. These observations concur with results of another study, which compared outcome in long-term surgically cured patients with medically controlled patients and

which showed better results in the first group (van Thiel et al 2005), suggesting that GH-suppressive therapy in its present form is unable to fully correct cardiac dysfunction. The impact of this finding on long-term mortality in acromegaly is unknown.

### Tumor growth

The anti-tumoral effects of somatostatin analogs are linked to the activation of the subtype receptors SSTR1, SSRT2, SSTR4, and SSTR5, which all induce cell cycle arrest. Apoptosis is associated with SSTR3 and possibly also with SSTR2 signaling (Danilla et al 2001; Bevan 2005). GH secreting adenomas express different somatostatin receptors, as shown for example by a recent study in which 77% expressed SSTR2, 69% SSTR1 and SSTR3, and 60% SSTR5. In the same study, lanreotide inhibited cell proliferation in vitro in 10 out of 13 adenomas (Florio et al 2003). Lanreotide also stimulates apoptosis as was found in surgically removed GH secreting adenomas to  $8.7 \pm 2.6\%$  in tumors compared with less than 3.5% in controls (Wasko et al 2003). The clinical response in terms of GH control and tumor size reduction correlates with the expression of somatostatin receptor subtype 2a (Fougner et al 2008; Taboada et al 2008). Preoperative treatment with lanreotide SR for 1–3 months in 104 acromegalic patients led to tumor size reduction in 66%, with a mean decrease of 152 mm<sup>3</sup>. A decrease in adenoma size of more than 20% was found in 29% of the patients (Lucas et al 2003). Other studies in which the decrease in adenoma size could be evaluated are listed in Table 7. In the meta-analysis of 14 clinical studies using somatostatin analogs as primary treatment, 36.6% of the patients exhibited a significant reduction in tumor size, with a weighted mean of 19.4% (Melmed et al 2005). Factors (not necessarily predictors) associated with tumor shrinkage after primary therapy with somatostatin analogs were post-treatment IGF-I, the age of the patient and the percentage GH decrease (Colao et al 2006a), and essentially confirming previously reported findings (Lucas et al 2003). In another meta-analysis of 44 trials, tumor shrinkage was related to the choice of the somatostatin analog. Octreotide LAR appeared to be more potent than lanreotide SR, with an odds ratio of 9.4 (Freda et al 2005). Preliminary data on biochemical remission of acromegaly after somatostatin analogs withdrawal suggest that some well-responsive patients might be cured, but long-term follow up is clearly needed (Ronchi et al 2008).

### Quality of life

QoL remains impaired in acromegaly even after successful pituitary surgery due to persisting joint-related complaints

(Biermasz et al 2005a). An early open study on the effect of lanreotide SR on QoL suggested a positive effect of treatment (Sonino et al 1999). However, in another study comprising 52 acromegalic patients no differences could be shown between lanreotide-controlled and noncontrolled patients using the AcroQoL, a questionnaire specifically developed for acromegaly. Interestingly, in the controlled group, surgically cured patients were much better off than patients controlled with lanreotide (Hua et al 2006). This observation underscores subtle differences between restoration of normal physiology and effective GH-suppressive medication, as found in intensive GH sampling studies in acromegalic cohorts (Biermasz et al 2004c). Finally, in a study of 93 patients with acromegaly control of GH and IGF-I had a positive impact on the subscale appearance, but overall QoL was severely impaired (Matta et al 2008).

### Predictors of clinical response

A priori conditions for a favorable clinical response to somatostatin analog therapy are the density and distribution of SSTR2a receptors in the adenoma (Lamberts et al 1996). It is controversial whether a single acute octreotide test can predict the clinical response during long-term treatment. In this respect 3 studies reported positive results (Biermasz et al 2005b; Gilbert et al 2005; Karavitaki et al 2005), whereas 3 others concluded that the test was not useful (Colao et al 1996; de Herder et al 2005; Prokajac et al 2005). The absolute height of pretreatment GH levels is obviously another important factor for the efficacy of treatment, and indeed several studies have demonstrated that tumor debulking procedures improved the clinical outcome of medical therapy (Colao et al 2006b; Karavitaki et al 2007).

### Primary pharmacologic treatment

Patients with a high chance of curative surgery should be offered this treatment. However, primary medical treatment should be considered in patients with a high surgical risk, patients with large invasive tumors and obviously in those who refuse surgery. Dose escalation with short-acting octreotide resulted in a better outcome in patients treated with octreotide as primary medication than those who received this drug as adjuvant medication after surgery (Newman et al 1995). Given as primary treatment, octreotide LAR controlled GH secretion in 57%, IGF-I in 45%, and caused tumor reduction of more than 50% in 44% out of 99 patients (Colao et al 2006a). This group and Cozzi and colleagues also found that dose escalating resulted in an even better outcome (Cozzi et al 2003; Colao et al 2007). Limitations

of these studies are that they are not randomized to primary surgery and that no data are available on long-term effects on survival.

Primary medical treatment may also be aimed at improvement of surgical outcome. Most of the studies addressing this issue had an open label design. Three studies reported beneficial effect on outcome (Barkan et al 1988; Colao et al 1997; Stevenaert and Beckers 1996), whereas three others did not (Biermasz et al 1999; Kristof et al 1999; Abe and Lüdecke 2001). Therefore, a conclusive statement cannot be made on this issue.

### Failures of medical therapy

As outlined above, somatostatin analog treatment will not control clinical symptoms and biochemical parameters in all acromegalic patients, and about half of them will still have raised IGF-I and/or GH levels. An increase in the injection frequency of lanreotide Autogel<sup>®</sup> to once every 2–3 weeks is generally not successful (Abrams et al 2007). Another, less expensive approach is to combine treatment with dopaminergic agonists (Freda 2003; Cozzi et al 2004). More effective is combined treatment with pegvisomant as demonstrated by a single center open labeled study. Long-term efficacy of combined treatment was demonstrated in 32 patients who all normalized IGF-I with pegvisomant in a dose of 40–160 mg given once weekly (24 patients) or twice weekly (Neggers et al 2007). Two large multicenter studies are respectively ongoing and complete, in which weekly administered pegvisomant is combined with lanreotide Autogel<sup>®</sup> in patients not controlled during treatment with 120 mg lanreotide Autogel<sup>®</sup> (ClinicalTrials.gov, NCT 00383708) and daily pegvisomant injections with octreotide LAR (ClinicalTrials.gov, NCT 0068029). Preliminary results of the latter study suggest equal efficacy in the two randomized parallel treatment groups towards serum IGF-I normalization, but with a higher incidence of side effects in the combined treatment group (Harris et al 2007). Considering the number of patients included, these studies will most likely answer questions about the efficacy of combined somatostatin analog and GH-receptor blockage in the treatment of acromegaly. However, both studies did not exclude previous surgery or radiation therapy, so that any conclusions drawn from these studies may not be applicable to primary medical treatment.

Due the favorable receptor binding profile, SOM230 (pasireotide) is likely to be a powerful somatostatin analog, which might be used in therapy-resistant cases to the registered somatostatin analogs (van der Hoek et al 2005; Ben-Shlomo and Melmed 2007). Clinical Phase II studies

in acromegaly are now being carried out in the US with both the short-acting form as well as the slow-release formulation (ClinTrial.gov NCT000088582, NCT00171730, and NCT00600886). Other somatostatin agonists currently developed were recently reviewed (Roelfsema et al 2006). Potential interesting drugs are chimeric somatostatin analogs. This class of drugs combines dopamine and somatostatin structural elements and retains affinity for specific somatostatin and dopamine receptor subtypes. These new drugs can not only suppress GH (and other pituitary hormones) better than currently clinically used drugs, but may also have much stronger antiproliferative actions, at least in vitro (Ferone et al 2007; Zatelli et al 2007).

## Summary and future perspectives

Lanreotide Autogel® is an exceptional pharmaceutical achievement, based on the unique property of self-aggregation of lanreotide. The formulation is delivered in prefilled syringes and can be easily injected without medical supervision by the patient or partner after proper training (Bevan et al 2008), whereas octreotide LAR requires qualified personnel for administration.

Lanreotide SR 30 mg/7–14 days can control serum GH in 59% and IGF-I concentrations in 49% of patients, while the results of the 60 mg formulation/4 weeks are 60% and 58%, respectively. Lanreotide Autogel® controls GH in 58% and IGF-I in 48% of patients. Compared with octreotide LAR the efficacy of lanreotide SR is less, although the differences are not large (Freda et al 2005). No large scale data are available for lanreotide Autogel®, a latecomer in this therapeutic field, for making a reasonable comparison with octreotide LAR.

The present formulations of somatostatin analogs can be classified as a second generation of effective GH-suppressive drugs, but these agents are clearly not adequate for all patients, depending on tumor somatostatin receptor status. New somatostatin analogs include SOM230, which is currently being used in several trials in the US, and the potentially very powerful chimeric drugs developed by Ipsen SA. The latter drugs, if successful in phase II–IV studies, will probably take another 5–10 years before becoming available for clinical use by endocrinologists. At present patients not controlled by somatostatin analogs should be treated with adjuvant pegvisomant, either as daily injections, as recommended by Pfizer, or as once-weekly or 2-weekly injections in a titrated dose, which data in the literature have suggested as sufficient (Feenstra et al 2005; Jørgensen et al 2005; Harris et al 2007; Neggers et al 2007). It is to be expected that other GH receptor blocking agents will become available

in the future, which might not have the potential drawbacks of pegvisomant (Roelfsema et al 2006).

## Disclosures

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