General introduction and aims of the thesis

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Review of current and emerging treatment options in acromegaly.

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Combined treatment of somatostatin analogues with pegvisomant in acromegaly.

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How to position pasireotide LAR treatment in acromegaly?

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This introductory chapter of the thesis will focus on the medical treatment of acromegaly. This is preceded by a brief description of the central and peripheral regulation of the GH-IGF-I axis with a focus on dysregulation of this axis in acromegaly.

PITUITARY GLAND PHYSIOLOGY

General characteristics

The pituitary gland is often called the "master gland" of the endocrine system, because its hormones play a central role in a vast array of physiological feedback functions such as growth, metabolism, energy balance, osmoregulation, and stress response (1). The normal pituitary gland is a bean-shaped gland with an average weight of 0.6 grams (figure 1). The gland is located inferior the hypothalamus within the sella turcica and linked to the hypothalamus via the pituitary stalk which contains a highly vascularized portal system. The pituitary is comprised of three anatomically and functionally distinct lobes, the anterior lobe (adenohypophysis), the intermediate lobe, and the posterior lobe (neurohypohysis). The anterior lobe contains five different hormone-secreting cell lineages which produce the following hormones:

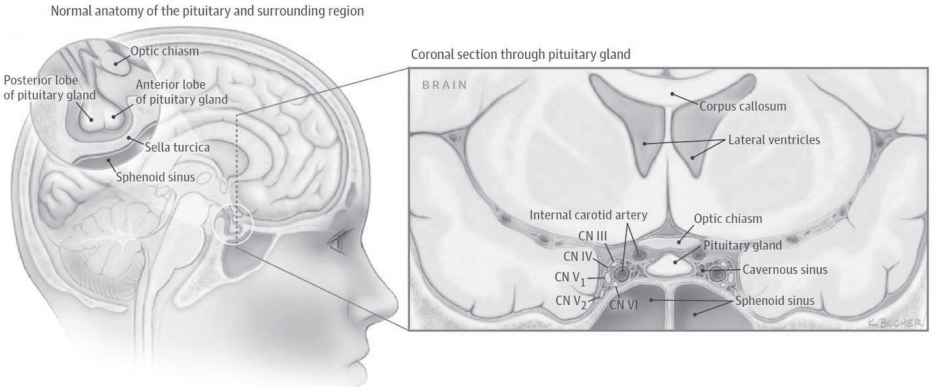

Figure 1. Normal anatomy of the pituitary gland.
Normal anatomy of the pituitary gland with its surrounding structures. The borders of the pituitary are composed of the sella turcica below (retrosellar), the optic chiasm above (suprasellar), and the cavernous sinuses on both sides (parasellar). The sella turcica is situated above the sphenoid sinus. The cavernous sinuses constitute a thin-walled venous network that receive blood from the superior and inferior ophthalmic veins, the sphenoparietal sinus, and the superficial middle cerebral veins. Structures crossing the cavernous sinuses lateral to the pituitary gland include the internal carotid artery, cranial nerve III (oculomotor), cranial nerve IV (trochlear), cranial nerve VI (abducens) nerve, two branches of cranial nerve V (trigeminal nerve branch 1 and 2), the ophthalmic branch V1, and the maxillary branch V2. Source: Molitch ME, Diagnosis and Treatment of Pituitary Adenomas: A Review, JAMA. 2017;317:516-524. Image reproduced with permission of the rights holder, JAMA.

the corticotrophs that produce adrenocorticotrophin (ACTH), the gonadotrophs that produce the gonadotrophins luteinizing hormone (LH) and follicle-stimulating hormone (FSH), the somatotrophs that produce growth hormone (GH), the lactotrophs that produce prolactin (PRL) and, the thyrotrophs that produce thyroid-stimulating hormone (TSH). The somatotrophs may also produces both GH and PRL. In addition, the anterior lobe also contains folliculo-stellate cells or pituicytes that are support cells (2). The intermediate lobe contains only α-melanotrophin (α-MSH). In humans this lobe is considered rudimental as it regresses at the 15th week of gestation. In contrast to the anterior lobe, the posterior consists of mainly neural projections from the hypothalamus that produces arginine, antidiuretic hormone (ADH, or vasopressin) and oxytocin.

Growth hormone

The somatotrophs, which synthesize, store and secrete GH, are the predominant cell type of the anterior pituitary, constituting about 45% of the pituitary cell population. GH is a single-chain 191-amino acid polypeptide and over 90% of GH in the circulation constitutes a 22 kilodaltons (kDa) molecule (3). About 50% of circulating GH is bound to GH binding protein (GHBP), which is the soluble version of the extracellular domain of the GHR, and is important for the bioavailability and bioactivity of GH (4, 5). Binding of GH to the GHR induces dimerization of the GHR and sets a intracellular signaling cascade in motion which leads to activation of the tyrosine kinase JAK2, which activates the STAT5, PI3K, and MAP kinase pathways (6-8).

Normal GH secretion occurs in a pulsatile circadian rhythm with the majority of its secretion occurring during deep sleep. During hypoglycemia and physical exercise GH secretion is amplified, while hyperglycemia and leptin suppress GH secretion (9-13). Circulating GH is high at 20 weeks of gestation, and subsequently falls during the neonatal stage and childhood until puberty, when GH secretion peaks to 2 mg/day, after which it declines progressively through aging (14).

GH is a pleiotropic hormone due to its involvement in the regulation of many physiological processes, such as growth, glucose, lipid and bone metabolism, reproduction, osmoregulation and the immune system. GH has both anabolic and catabolic actions. Most of the anabolic actions of GH are mediated via IGF-I. GH is the primary regulator of IGF-I production (15). GH is mainly a catabolic hormone during fasting and in the absence of IGF-I but becomes anabolic in the presence of IGF-I after food intake. The most well-known (anabolic) action of GH is stimulation of cellular growth and differentiation. The catabolic actions of GH derive from its lipolytic effects on adipose tissue. GH administration stimulates lipolysis and inhibits lipogenesis which results in

elevated free fatty acids (FFAs), whereas GH deficiency is associated with increased lipid mass. GH is a counter-regulatory hormone that antagonizes the effects of insulin, while IGF-I promotes insulin sensitivity (16, 17). Therefore, GH and IGF-I display opposing effects on insulin homeostasis.

Growth hormone-pituitary-hypothalamus axis

Central GH secretion is positively regulated by the hypothalamus through GH releasing hormone (GHRH) and acylated ghrelin (AG) which stimulate GH secretion, and negatively regulated by somatostatin (somatostatin release inhibiting factor, SRIF) which inhibits GH secretion (Figure 2). The peripheral actions of GH are

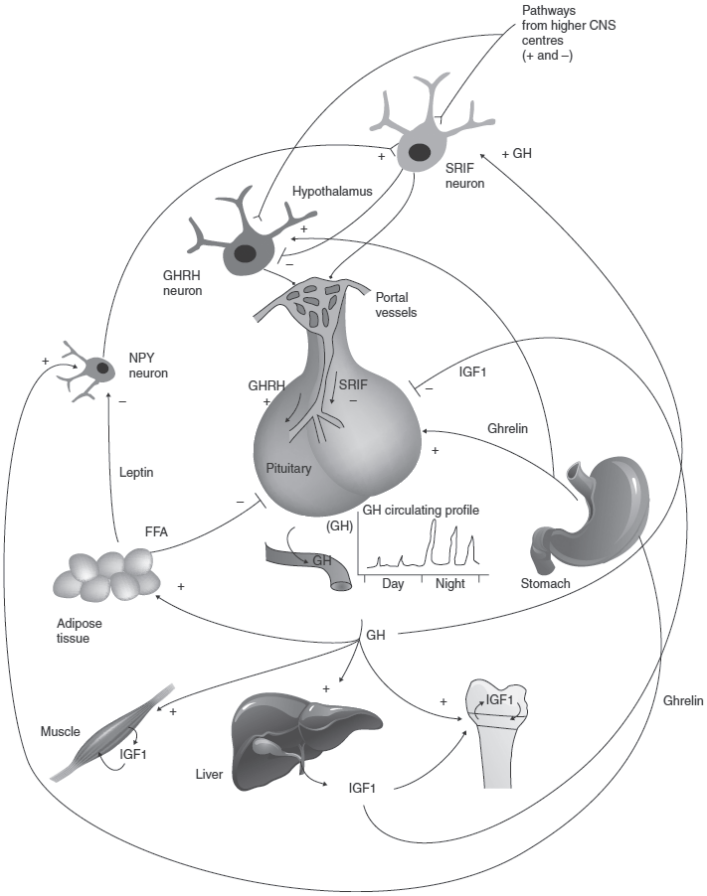

Figure 2 Central and peripheral components that regulate the GH axis.
Central and peripheral components that regulate the GH axis. NPY, neuropeptide Y; FFA, free fatty acids; GH, growth hormone; IGF1, insulin-like growth factor 1; GHRH, GH-releasing hormone; SRIF, somatotrophin release inhibitory factor. Image reproduced with permission of the rights holder, JAMA.

predominantly mediated via hepatic IGF-I production, but also through direct actions on local tissues.

Ghrelin

Ghrelin was discovered in 1999 by the group of Kojima and Kangawa as the endogenous ligand of the GH secretagogue receptor type 1a (GHSR1a). Ghrelin is a 28-amino acid peptide hormone secreted mainly from neuroendocrine X/A cells in the stomach (18, 19), circulating as both acylated ghrelin (AG) and unacylated ghrelin (UAG) isoforms (20). Unique to AG is the *n*-octanoyl acylation by the enzyme ghrelin O-acyl transferase (GOAT) at its serine-3 residue. In the circulation AG is rapidly deacylated by carboxylesterases into UAG (21). After binding to GHSR1a, AG potently stimulates pituitary GH secretion and food intake (orexigenesis). Inversely, GH itself inhibits AG secretion (22-25). But there are also conflicting reports on the interaction between ghrelin and GH, indicating that the physiological role of ghrelin in the regulation of GH secretion is not fully understood (26-29). Although AG was initially discovered as a GH secretagogue, it is now recognized as a multifunctional hormone, as it can modulate gut motility, stress response, sleep, learning, memory, cellular proliferation, differentiation and survival, immune response, energy homeostasis, glucose homeostasis, and insulin secretion (29, 30). UAG has several biological functions which are mediated independently from the GHSR1a receptor, and metabolic actions that counteract AG action. For example, AG displays diabetogenic actions such as suppression of glucose-stimulated insulin secretion and insulin sensitivity (31-38), while UAG shows the opposite (30, 31, 39). Although much work has been done, the cognate receptor(s) for UAG has yet to be identified. More about ghrelin is written in chapter 6 of this thesis.

ACROMEGALY

History

Acromegaly is a severe systemic disease most commonly caused by a benign GH-secreting (somatotroph) pituitary adenoma leading to excessive GH and IGF-I levels (40). Excessive GH secretion causes gigantism if it occurs prior to epiphyseal fusion and acromegaly after this time. The term acromegaly is from Greek meaning “large extremities”, and was originally named by the French neurosurgeon Pierre Marie in 1886, who provided the characteristic clinical description the disease (41). However, many other physicians before Marie have described acromegaly (42, 43). In 1567 the Dutch surgeon Johannes Wierus provided probably the first reliable medical description of acromegaly and gigantism (44).

Epidemiology

According to recent epidemiologic data, the estimated incidence of acromegaly is 1.8-13.7 cases per 100.000 people and the annual incidence is 0.2-1.1 cases per 100.000 people (45-51). The diagnosis of acromegaly is usually made in the fifth decade of life. The duration of symptoms until diagnosis is considerable with a median diagnostic delay of 5 years with some delays of over 15 years have been reported (47, 48, 52, 53). Many cases go unreported due to the insidious presentation and the lack of awareness of acromegaly among physicians.

Pathology

Acromegaly is almost always (≥95%) caused by a somatotroph adenoma. In very rare cases acromegaly may be caused by extrapituitary GH or GHRH hypersecretion from a pancreatic islet-cell tumour, bronchial carcinoid, or non-Hodgkin's lymphoma (54-59). Somatotroph adenomas can be classified as densely and sparsely granulated subtypes based on their appearance under an electron microscope. Sparsely granulated somatotroph adenomas (SGSA) are characterized by a more aggressive clinical behavior than densely granulated somatotroph adenomas (DGSA), as they are more likely to represent invasive macroadenomas which express lower somatostatin receptor subtype 2 (SST_2) protein expression and are resistant to first-generation long-acting somatostatin receptor ligand (SRL) therapy (60-63).

Clinical manifestations

The manifestations of acromegaly are due to the local effects of the pituitary tumour or the peripiheral actions of chronic GH and IGF-I hypersecretion (table 2). Central manifestations are mainly caused by large invasive macroadenomas and include headache, visual field defects due to impingement of the optic chiasm, cranial nerve palsy due to impingement of cranial nerves III, IV, and VI causing diplopia, or nerve V leading to trigeminal facial pain. Peripheral manifestations include soft tissue hypertrophy leading to characteristic enlargement of the hands, nose, forehead, eyebrow, jaw and feet. Clinicians should be aware of the possibility of acromegaly in patients with two or more of the following comorbidities: new-onset diabetes, diffuse arthralgias, new-onset or difficult-to-control hypertension, cardiac disease including biventricular hypertrophy and diastolic or systolic dysfunction, fatigue, headaches, carpal tunnel syndrome, sleep apnea syndrome, diaphoresis, and loss of vision (64).

Active acromegaly unmasks the diabetogenic effects of GH. Prolonged exposure to GH and IGF-I leads to insulin resistance and overt diabetes. In the general population insulin resistance and diabetes are associated with increased body fat, which is hallmark of the metabolic syndrome. However, many patients with acromegaly present

with insulin resistance and diabetes despite having a “favourable” body composition with a decreased body fat mass and increased muscle mass (65, 66).

Uncontrolled acromegaly is associated with a reduced life expectancy. If patients achieve biochemical control life expectancy is similar to the general population, despite this many patients with acromegaly have a reduced quality of life (QoL) (40, 67). Active acromegaly is associated with increased mortality. Normalization of GH and IGF-I levels largely reduces mortality to that of the general population (68).

Diagnosis

The biochemical diagnosis of acromegaly is based on demonstration of autonomous GH hypersecretion and elevated serum IGF-I levels. Due to the pulsatility and the short half-life of GH, concentration of GH may be undetectable in acromegaly patients (69). Measurement of single random GH levels is therefore not recommended. In contrast, serum IGF-I levels are relatively stable and show a log-linear correlation with GH (70), and have a long half-life of about 15 hours. In addition, IGF-I can be measured independent of time of the day and food intake. IGF-I serves as the integrative biomarker of GH secretion. A normal IGF-I within the age adjusted normal limits effectively excludes the diagnosis of acromegaly. However, in non-clear cut cases with IGF-I levels just above or around the upper limit of normality, confirmation is required by showing a lack of suppression of GH to less than 1 µg/L following a documented hyperglycemia during an oral glucose tolerance test (OGTT) (64). In acromegaly patients with poorly controlled diabetes mellitus the oral glucose tolerance test is not reliable and serum IGF-I levels should be re-assessed when glycemic control has been established. Systemic illnesses, hepatic or renal failure, malnutrition, diabetes mellitus and oral oestrogens may decrease IGF-I levels which might result in false-negative interpretations (64, 71, 72). False-positive elevated IGF-I levels can occur during pregnancy. Large variability inter-individual and intra-individual variability exists between the different IGF-I immunoassays (73). When monitoring IGF-I levels over time, it is recommended that the same immunoassay is used from laboratories that adhere to the international performance standards and use the appropriated normative data (74).

Following biochemical diagnosis, contrast enhanced magnetic resonance imaging (MRI) of the sellar region is required to assess tumour size, localization and invasiveness. A clinically relevant distinction which affects the surgical cure rates is microadenomas (≤1 cm) and macrodenomas (≥1 cm), invasiveness in the cavernous sinus, and impingement of the optic chiasm. In adenomas close to the optic chiasm visual fields assessment should be performed.

Treatment modalities

Surgery

Transsphenoidal surgery is the primary treatment for patients with small and, therefore, curable tumours or for large adenomas causing impingement of the optic chiasm (75, 76). Surgical results depend on preoperative GH and IGF-I levels, tumour

Table 1. Different clinical manifestations of acromegaly

Clinical manifestations of acromegaly	
Local tumour effects	*Somatic*
Visual field defects	Acral enlargement
Headache	Frontal bossing
Cranial nerve palsy	Prognathism
	Macrognathia
Metabolic	Diastema
Impaired glucose tolerance	Carpal tunnel syndrome
Hyperinsulinemia and insulin resistance	Arthralgias
Diabetes mellitus	Osteoarthritis
	Decreased bone quality
Lipids	Vertebral fractures
Hypertriglyceridemia	Myopathy
Endocrine - hypopituitarism	*Visceromegaly*
Erectile dysfunction	Goitre
Galactorrhoea	Macroglossia
Amenorrhea	Hepatomegaly
Secondary thyroid deficiency	Splenomegaly
Secondary adrenal deficiency	Renal hypertrophy
Cardiovascular	*Mineral*
Hypertension	Hypercalciuria
Arrhythmias	Hyperphosphaturia
Cardiomyopathy	Increased levels 25-hydroxyvitamin D3
Ventricular hypertrophy	
Congestive heart failure	*Renal*
	Increased aldosterone levels
Pulmonary	Nephrolithiasis
Central and obstructive sleep apnoea	
	Psychological
Dermatological	Impaired quality of life
Skin tags	Decreased self-esteem
Hyperhidrosis	Depression
Acanthosis nigricans	
Gastrointestinal	
Adenomatous colon polyps	
Dolichocolon	
Neuropsychological	

invasiveness and surgical skills. Surgery is the treatment of choice for microadenomas and well-defined intrasellar macroadenomas. In these cases experienced surgeons can achieve remission rates of about 80%, defined as postoperative normalization of IGF-I levels and suppression of GH levels to < 1 mg/l after an oral glucose load. These rates can drop to 20-30% for macroadenomas. For macroadenomas that are not entirely surgically resectable (eg, those with cavernous sinus extension) surgery may be considered with the goal of debulking the tumour mass. Debulking seems to increase the efficacy of postoperative treatment with SRLs (77-79), although conflicting data were reported as well (80). Preoperative treatment of macroadenomas with SRLs has been shown to improve surgical outcome (81-84). Successful surgery is accompanied by a rapid fall in GH and IGF-I levels and the costs are relatively low compared to life-long drug therapy, although the efficacy of surgery might be overestimated as the data on surgical outcome are almost exclusively reported from high specialist centers. In the United Kingdom, an efficacy rate for microadenonomas < 37% and for macroadenomas < 20% has been reported, for all centres together (85).

Radiotherapy

During the early 1900s radiotherapy was the treatment of choice for acromegaly (86, 87). To date, radiotherapy (RT) is considered a third line of treatment for acromegaly in most centres. Currently, RT is recommended for patients with residual tumour mass following surgery and medical therapy, and if medical therapy is not tolerated, unsuccessful, or unavailable (88-90). The method with the longest experience is conventional radiotherapy (CRT). CRT is administered in 20-30 fractions with a total dose of 40-45 Gray (91). CRT induces remission in about 50% of patients after a follow-up of 10 years. However, radiation-induced hypopituitarism is the main side-effect of all types of CRT, as 50-80% of patients develop pituitary insufficiencies within 5 to 10 years (92-94). Another drawback is that it takes sometimes years before RT induces biochemical remission, which comes along with a negative impact on quality of life (95). Analyses of the UK acromegaly database showed that CRT was associated with an increased mortality risk, and cerebrovascular disease as the main cause of death (96). Additionally, studies assessing QoL observed a lower QoL in patients treated with CRT that further decreased during follow-up (95, 97, 98). Joint problems are important factors affecting the QoL after radiotherapy (97). Other rare but severe side-effects of CRT include, optic neuropathy, radiation-induced cerebral tumours, cerebrovascular disease, and regrowth of pituitary adenomas. Stereotactic radiosurgery (SRS) methods has been developed with the aim to provide more precise targeting of the tumour and therefore less targeting of healthy brain tissue. SRS may be more safe than CRT, but long-term studies evaluating safety are lacking at the moment (99).

Medical therapy

Dopamine agonists

Under normal physiological conditions dopamine stimulates GH secretion (100, 101). However, in the 1970s it was discovered that administration of L-DOPA paradoxically reduced GH hypersecretion in patients with acromegaly (102). Subsequently, dopamine receptors (DR) were found on somatotroph adenomas (103). Of the 5 distinct DR subtypes, the D2 receptor (DR2) is the predominantly expressed DR subtype (104, 105). Until the 1980s dopamine agonists (DA) have been the only class of pharmaceutical agents available for acromegaly. Bromocriptine is a first-generation DA which normalized IGF-I levels in only about 10% of patients (106). Cabergoline is a second-generation ergot derivative DA with a high affinity for DR2, and has been used as monotherapy and in combination with SRLs (107). Due to its higher efficacy and better tolerability it has replaced bromocriptine as the DA of choice for treatment of hyperprolactinemia. Because cabergoline has a modest efficacy of about 30% in normalizing only IGF-I levels (< 1.5 x ULN) (88, 108). Cabergoline monotherapy is considered a good add-on therapy in patients with partial response to SRLs, and for patients with no access to pegvisomant (107, 109). Cabergoline can be taken orally and is inexpensive. It has a favourable safety profile, the adverse effects of cabergoline are considered mild and include postural hypotension, headache and nausea (110). Seldomly, psychological symptoms such as psychosis and impulse control disorders have been reported (111-113). Furthermore, long-term use of very high doses of cabergoline (3.5 mg/day) has been linked to valvular heart disease in patients with Parkinson's disease (114, 115). Although patients with acromegaly use much lower doses of cabergoline, active acromegaly itself is associated with increased risk of valvular heart disease (116-119). However, latest data from a longitudinal study showed no increased risk between cabergoline-treated acromegaly patients and a matched control population with untreated acromegaly (120).

Somatostatin receptor ligands

Somatostatin (SST or SRIF) was discovered in 1973 by the group of Roger Guillemin as the first hypothalamic hormone to regulate GH secretion (121). Somatostatin exerts inhibitory effects on hormone secretion from the pituitary, pancreas and the gastrointestinal tract (122). SST is a cyclic peptide with two active isoforms present in the circulation, SRIF-14 and SRIF-28. The biological effects of SST are mediation by its binding to five G protein-coupled receptor (GPCR) subtypes of somatostatin receptors (SSTs) (123, 124). SST are widely expressed in tissue specific patterns. In the normal human foetal pituitary gland all five SSTs expressed, but SST_2 and SST_5 are most important for regulation of hormone secretion (125). Somatotroph

adenomas mainly express SST_2, SST_5 and to a lesser extent SST_1 (126-131) (table 1). In the pancreas SST is an important regulator of glucose homeostasis, as it tightly regulates the secretion of insulin, glucagon and GLP-I. α-cells which produce glucagon express mainly SST_2, ß-cells which produce insulin express predominantly SST_5 and to a lesser degree SST_1, and δ-cells which produce SSTR-14 express mainly SST_5. Furthermore, enteroendocrine L-cells located in the ileum and colon, which produce GLP-I express mainly SST_5 (132-135).

Although native SST has potent anti-proliferative and anti-secretory effects on different tissues, it is clinically not useful due to its very short half-life of less than 3 minutes and the post-infusion rebound phenomenon (136). These limitations have been overcome by the development of more stable somatostatin receptor ligands (SRLs) which have a longer half-life and increased affinity for SSTRs. The short-acting immediate release SRLs, octreotide (137) and lanreotide (138) were initially developed. These first-generation SRLs show preferential binding to SST_2 and have an increased half-life of about 2 hours allowing for multiple daily injections. To date, more practical long acting depot formulations octreotide Long Acting Release (octreotide LAR) and lanreotide autogel (lanreotide ATG) are used which allow for 4 weekly injections. Both formulations are equivalent in terms of efficacy, but differ in their mode of administration; lanreotide is available in pre-filled syringes injected deep subcutaneously and octreotide LAR requires reconstitution before being injected intramuscularly (139, 140). First-generation SRLs represent the first line medical treatment for acromegaly (141). High SST_2 protein expression of the somatotroph adenoma is the main pathophysiological rationale for their efficacy in acromegaly. Biochemical normalization of IGF-I and GH levels can be achieved in about 40% of treatment-naïve patients with SRLs (142, 143). Clinically relevant tumour volume reduction of over 20% is frequently observed (40-63%) during SRL treatment and the decrease in GH levels generally occurs within the first 4 months (143-147). SRLs have a favourable safety and tolerability profile. Relatively few side effects do occur; in the first few weeks transient mostly self-limiting gastrointestinal complaints such as abdominal discomfort, nausea and steatorrhea occurs in most patients (148). Asymptomatic gallbladder stones or bladder sludge can develop in the first 18 months in up to 20% of patients (149). In 2018, Cozzolino and co-workers published a large meta-analysis of 47 prospective interventional trials studying the effect of first generation SRLs on glucose homeostasis in 1297 patients with acromegaly (150). The authors show that both lanreotide ATG and octreotide LAR significantly reduced insulin secretion which was not (completely) counterbalanced by the reduction in GH and IGF-I levels (150). In general, the net effect of SRLs on glucose metabolism is considered marginal, but it is clinically relevant in patients with insulin resistance and overt diabetes.

Pegvisomant

The GH molecule has two sites which interact with the extracellular region of the GHR performed dimer. Site 1 of the GH molecule interacts with one the GHRs and then GH site 2 interacts with the other GHR which leads to a functionally dimerized complex that induces GH-dependent intracellular signalling (152). Glycine at position 120 of the third alpha helix in binding site 2 of GH is crucial for GH action. In the early 1990s it was discovered that substitution of this glycine by lysine blocks intracellular signalling, converting GH into a GHR antagonist (153). Additional mutations in binding site 1 increased the affinity of PEGV to the GHR. Due to the short half-life of GH, the GHR antagonist was PEGylated by covalent addition of 4 to 6 5-kDa linear polyethylene glycol (PEG) molecules, extending the half-life to about 70 hours, which resulted in the marketed drug pegvisomant (PEGV; Somavert®) (154). PEGV itself can form dimers with the GHR and is internalized by the GHR, but does not induce GH-dependent intracellular signalling (155). Recently it has been shown that PEGV also inhibits GHR nuclear localization (156).

PEGV was approved in the United States in 2003 followed by approval in Europe in 2004 (154, 157). It is currently used as a second line therapy in patients that are inadequately controlled with SRLs monotherapy (88). Early clinical trials demonstrated IGF-I normalization in over 90% of patients resistant to SRL (158-160). Because PEGV is a competitive GHR blocker, virtually all patients with acromegaly can be controlled provided that the treating physicians adequately titrate the dose of PEGV. More recent real-life registry studies showed lower IGF-I remission rates of 60-70% (161-163), which is mainly attributed to an inadequate dose titration of PEGV.

Table 1. SST expression in normal pituitary and in somatotroph adenoma. Binding affinities of the difference somatostatin analogues to the five somatostatin receptor subtypes (SST_{1-5})

	SST_1	SST_2	SST_3	SST_4	SST_5
Somatotroph adenomas	60% +	95% +++	45% +	<5% –	90% ++
Somatostatin receptor ligands					
SRIF-14	0.1-2.26	0.2-1.3	0.3-1.6	0.3-1.8	0.2-0.9
Octreotide	280	0.38	7.1	>1000	6.3
Lanreotide	180	0.54	14	230	17
Pasireotide	9.3	1.0	1.5	>100	0.16

The percentage somatostatin receptor subtype (SSTR) expression and the quantitative estimation of receptor expression in somatotroph adenomas. In the rows below the binding affinities of endogenous somatostatin and the different somatostatin analogues is shown, expressed as IC_{50} values nmol/L (124, 136, 151).

Treatment with PEGV results in a rapid fall of serum IGF-I levels which usually leads to a paradoxical rise of serum GH levels, due to the negative feedback loop via the hypothalamus and the pituitary (159, 164). Cross-reactivity between PEGV and endogenous GH in commercial assays disables proper assessment of the endogenous GH levels (165). For these reasons GH cannot be reliably assessed in patients treated with PEGV, unless specific assays are used (166). Therefore, the key biomarker during the treatment of PEGV are serum IGF-I level with specific signs such as ring-size and body fat mass.

SRL and PEGV combination treatment

Because the majority of acromegaly patients are resistant to SRLs, additional therapies are required to achieve control of disease activity. Combining SRLs with PEGV combination treatment has several advantages because of their different mode of action. The first advantage of combination treatment is the much lower (around 50%) required weekly dose of PEGV (164). Because SRLs inhibit GH secretion, PEGV encounters less competition of endogenous GH around the GHR resulting in a lower necessary dose of PEGV to block all GHRs during combination therapy and additionally reduces the number of GHRs on the hepatocytes (164, 167, 168). In addition, combination treatment induces a 20% increase in PEGV serum levels than during PEGV monotherapy (169). The underlying mechanism for the observed rise in PEGV serum levels remains unknown (170). Besides direct inhibition of pituitary GH secretion, which leads lower hepatic IGF-I production, SRLs have also non-pituitary action on IGF-I production. SRLs can indirectly suppress hepatic IGF-I production by reducing portal insulin levels, which leads to a reduction in hepatic GHR expression (171). In addition, data from rodent studies has demonstrated that somatostatin can also directly suppress hepatic IGF-I production and possibly receptor-mediated clearance of GH (172). Taken together, these data suggest that SRLs induce a state of GH resistance in the liver, while peripheral extra-hepatic tissues might still be exposed to GH excess. Blocking peripheral GH action using PEGV can therefore be useful in treating extra-hepatic acromegaly (173). Based on this concept *Neggers et al* demonstrated in a prospective double blind placebo controlled crossover study that low doses of PEGV may improve quality of life in patients controlled with SRL monotherapy (174). Furthermore, PEGV is the treatment of choice for acromegaly patients with insulin resistance or diabetes, as it has beneficial effects on glucose metabolism. PEGV improves hepatic and peripheral insulin sensitivity, reduces hepatic gluconeogenesis and reduces free fatty acids (175-180).

Safety

The most common adverse events associated with the use of PEGV are transient elevated liver transaminases (TETs) >3 times the upper limit of normal which seemed to occur more frequently during combination treatment (162, 164, 167, 168, 181). Although many risk factors have been brought forward, the underlying pathophysiology of PEGV-induced TET development remains unclear (167, 168, 182, 183). The incidence of lipodystrophy at the injection site was reported in 3% of patients, but is clinically not significant as it regresses in most patients when PEGV is discontinued (184). Initially there were concerns that the reduced pituitary feedback inhibition from GH blockade would stimulate growth of the pituitary tumour (remnant). However, there is currently is no clear evidence that PEGV causes a clinically significant increase in tumour size. Therefore, PEGV can be considered as a safe approach, especially when combined with SRLs

Pasireotide

Pasireotide long-acting release (PAS-LAR) was approved by the FDA and EMA in 2014 and is the only second-generation SRL on the market. Pasireotide is a stable cyclohexapeptide showing high affinity to multiple SSTRs, with the highest affinity to SST_5 followed by SST_2, SST_3 and SST_1 compared with SRIF, octreotide and lanreotide (151). The higher affinity for SST_5 (and to other SSTRs) forms the pathophysiological rational for the use of pasireotide in acromegaly. Besides its broader SSTR binding profile, pasireotide has unique functional post-receptor effects. SSTR activation and trafficking are modulated in a manner distinct from SRIF and octreotide. Pasireotide shows lower SST_2 internalization, less ß-arrestin mobilization and lower activation of second messenger pathways such as lower activation of ERK pathway, less increase of intracellular Ca^{2+} and less cAMP inhibition (185-187). Therefore, pasireotide is considered to be a biased agonist for SST_2.

Efficacy

Two phase III studies reported the efficacy of PAS-LAR treatment in acromegaly (188, 189). The C2305 trial was double blind randomized head-to-head superiority study between PAS-LAR and octreotide LAR in medically naïve acromegaly patients (190). After one year of treatment, IGF-I normalization was achieved in significantly more patients using PAS-LAR (38.6%) than octreotide LAR (23.6%). However, GH reduction (≤2.5 g/L) was similar between patients using PAS-LAR (48.3%) and octreotide LAR (51.6%) (190). In the PAOLA study patients with acromegaly who were inadequately controlled despite ≥ 6 months treatment on maximum doses of first-generation SRLs were randomly assigned to pasireotide LAR at 40 mg, 60 mg, or continued on their treatment with octreotide LAR or lanreotide ATG (active control) (189).

After 24 weeks, biochemical control was achieved by 15% of patients using pasireotide LAR 40 mg and 20% using PAS-LAR 60 mg, compared with no patients in the active control group (189).The extension phase of both studies showed comparable response rates (191, 192). Also, about 17% of the patients with inadequate biochemical control after 12 months of treatment with octreotide LAR, achieved biochemical control after switching to PAS-LAR treatment (193). Although the effects of PAS-LAR and octreotide LAR treatment on the reduction of GH levels were superimposable in the C2305 study, PAS-LAR treatment was more effective in lowering IGF-I levels (188, 194).

Tumour volume reduction

Results from a phase II study in 61 patients with active acromegaly showed that treatment with short-acting pasireotide resulted in clinically significant (>20%) tumour volume reduction in 39% of patients after 3 months of treatment, which increased to 54% after 6 months of treatment (195). However, in the C2305 study PAS-LAR and octreotide LAR treatment were equally effective in reducing tumour volume (188). In the PAOLA study, tumour volume reduction occurred more frequently in patients using PAS-LAR 40 mg (19%) and 60 mg (11%), than in patients in the active control group (2%) (189). This finding is not entirely surprising because it is plausible that patients who were inadequately controlled with first-generation SRLs are more likely to respond to PAS-LAR treatment than medically naïve patients. The mean decrease in tumour volume during the extension study was 25% for crossover to PAS-LAR and 18% for crossover to octreotide LAR, while 54% of PAS-LAR treatment and 42% of octreotide LAR patients achieved significant tumour volume reduction (193). Taken together, these clinical studies suggest that PAS-LAR might exert a greater effect on tumour control in patients that show no tumour shrinkage after first-generation SRL treatment. In addition, patients with large tumours due to genetic causes such aryl hydrocarbon receptor-interacting protein (AIP) mutations and X-linked acrogigantism are frequently resistant to first-generation SRL, and could therefore be more responsive to PAS-LAR treatment (196-198).

Quality of life and symptoms

In medically naïve patients, PAS-LAR and octreotide LAR showed similar improvements in acromegaly symptoms score (188). In the PAOLA study, the patients in the PAS-LAR treatment groups showed more improvement in acromegaly symptoms than patients in the active control group (189). As mentioned above, the observed improvement in acromegaly symptoms in the PAS-LAR treatment groups was to be expected. Nevertheless there is evidence that pasireotide has an analgesic effect on headache symptoms of acromegaly patients (190, 199-201).

Safety

PAS-LAR is generally well-tolerated and has a comparable safety profile to first-generation SRLs, except for a greater frequency and degree of hyperglycemia-related adverse events (188, 189). Hyperglycemia-related adverse events were reported in 57.3% of patients treated with PAS-LAR and in 21.7% of patients treated with octreotide LAR in the C2305 study (188). In the PAOLA study, hyperglycaemia-related adverse events occurred in 65% of patients treated with pasireotide LAR and 30% of patients in the active control group (189). Hyperglycaemia occurred early after drug initiation, with fasting plasma glucose (FPG) and glycosylated haemoglobin (HbA1c) levels increasing in the first 3 months, and plateauing thereafter with additional antidiabetic medication (192). In the ACCESS study, designed to assess the safety of PAS-LAR treatment in patients with acromegaly, hyperglycaemia-related adverse events were reported in 46% of patients and about 9% discontinued PAS-LAR because of hyperglycaemia (202). Predictors for pasireotide-induced hyperglycaemia were higher baseline glucose levels (FPG >5.55 mmol/l) and patients receiving antidiabetic medication (203). Mechanistic studies in healthy volunteers have revealed that pasireotide inhibits secretion of insulin, glucagon-like peptide I (GLP-I) and gastric inhibitory polypeptide (GIP), and modestly suppresses glucagon secretion. However, pasireotide did not affect hepatic or peripheral insulin sensitivity as evaluated with the hyperinsulinaemic-euglycaemic clamp test and OGTT (204, 205). The effects of pasireotide on insulin, glucagon and incretin secretion can be explained from its SSTR binding profile. SST_5 is known to be expressed on pancreatic ß-cells which mediate insulin secretion, but also on enteroendocrine L-cells which produce GLP-I (132-134). In contrast SST_2 is mainly expressed on pancreatic α-cells which mediate glucagon secretion (206, 207), which may explain the modest effect of pasireotide on glucagon secretion.

Scope and Aims of the Thesis

Over the last decade SRL and PEGV combination treatment has been established as an effective and safe second line treatment modality for acromegaly patients with inoperable pituitary adenomas and who are refractory to medical treatment. In the Rotterdam cohort over 90% of patients achieved IGF-I normalization with combination treatment. Despite this high efficacy, PEGV poses an economic burden due to its high treatment costs. Furthermore, 4 weekly SRL injections and daily to weekly PEGV injections may negatively impact long-term adherence and quality of life of patients. With the goal to improve patient adherence we hypothesized that it is possible to temporarily withdraw SRL treatment in patients using combination treatment. Therefore, in **Chapter 2** we aimed to determine the efficacy of temporary withdrawal of SRL treatment and switch to (twice) weekly PEGV monotherapy in patients controlled with combination treatment. For how long can biochemical control be maintained without a need to increase the PEGV dose?

As PAS-LAR has demonstrated superior efficacy over first-generation SRL and is approved a second line medical treatment for acromegaly, the question arises what the position is of PAS-LAR in relation to PEGV in the modern medical management of acromegaly. Switching from SRL and PEGV combination treatment to PAS-LAR could lead to a reduction in the PEGV dose required to control disease activity. A lower PEGV dose and/or less PEGV injections (i.e. PEGV sparing effect) could contribute to an improvement in quality of life and patient convenience. What is the safety of PEGV and PAS-LAR combination treatment? Especially with respect on glucose metabolism? What are predictors for pasireotide-induced hyperglycaemia? To address these questions we conducted the Pasireotide LAR and PEgvisomant (PAPE) study, a prospective single-centre open-label trial to study the efficacy and safety of switching to PAS-LAR alone or in combination with PEGV in patient who were well-controlled with SRL and PEGV combination treatment. In **Chapter 3** the 24-weeks efficacy and safety results (PAPE core study) are presented.

Chapter 4 focuses on the results of the extension phase until 48-weeks results. The main goal of the extension phase was to find the optimal PAS-LAR and PEGV dose to achieve IGF-I normalization. In addition, we aimed to investigate whether baseline insulin secretion as measured with the OGTT correlates with hyperglycaemia after PAS-LAR treatment during the study.

Based on the results of PAPE study we aimed to investigate in active acromegaly, whether the responsiveness to PAS-LAR treatment during the PAPE study correlated with the previous responsiveness to SRL monotherapy in the same patients. Secondly,

we assessed to what extent SST_2 and SST_5 protein expression on somatotroph adenoma were correlated to responsiveness to PAS-LAR treatment. It has previously been suggested that SST_5, and not SST_2, protein expression of the somatotroph adenomas predicted responsiveness to PAS-LAR treatment (208, 209). In **Chapter 5** aimed to confirm whether this is indeed the case in our cohort of patients included in the PAPE study.

Ghrelin is an important peptide hormone regulated by the GH-axis and is modulated by medical treatment. In acromegaly SRL treatment reduces ghrelin levels, while PEGV treatment increased ghrelin levels. It is however unknown what the net effect of SRL and PEGV combination treatment is on ghrelin levels in acromegaly patients. Previous studies have only measured total ghrelin using unspecific radioimmunossay methods and have not distinguished between AG and UAG levels. Therefore, in **Chapter 6** we aimed to assess plasma AG and UAG levels, and the AG/UAG ratio in acromegaly patients on SRLs and PEGV combination treatment, compared with the control groups using PEGV monotherapy and medically naïve patients.

PEGV is approved for the medical treatment of acromegaly since 2003. Patients are long-term exposed to high doses of PEG compared with other PEGylated biological drugs. Little is known about how PEGV is cleared from the body and which type of cells are involved. We postulated that PEGV is cleared by the mononuclear phagocyte system (MPS) because PEG is considered to be a non-biodegradable molecule. Kupffer cells are the most important macrophages of the MPS and have been reported to clear PEGylated nanomaterials in a previous study. In **Chapter 7** we presented the finding of a pilot study in which we assessed in two acromegaly patients whether PEGV is expressed in the liver, and if so whether Kupffer cells are involved in the clearance of PEGV using immunofluorescence studies.

Chapter 8 provides a summary of the generated data, critically reviews the strengths and limitations of the aforementioned studies and brings forward future perspectives of outstanding questions. The discussion section is ended by presenting our clinical recommendations on the position of PAS-LAR in the modern medical management of acromegaly.

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