Somatostatin analogues in acromegaly and gastroenteropancreatic neuroendocrine tumours: past, present and future

Kjell Öberg[1] and **Steven W J Lamberts**[2]

[1]University Hospital, Uppsala, Sweden
[2]Erasmus Medical Center, Rotterdam, The Netherlands

Correspondence should be addressed to K Öberg
Email
kjell.oberg@medsci.uu.se

Abstract

Acromegaly is a hormonal disorder that arises when the pituitary gland secretes excess growth hormone (GH), which in turn stimulates a concomitant increase in serum insulin-like growth factor 1 (IGF-1) levels. Gastroenteropancreatic neuroendocrine tumours (GEP-NET) constitute a heterogeneous group of tumours that can secrete serotonin and a variety of peptide hormones that may cause characteristic symptoms known as carcinoid syndrome or other symptoms and hormonal hypersecretion syndromes depending on the tumour's site of origin. Current medical therapy for the treatment of acromegaly and GEP-NET involves the administration of somatostatin analogues that effectively suppress excess hormone secretion. After its discovery in 1979, octreotide became the first synthetic biologically stable somatostatin analogue with a short-acting formulation of octreotide introduced into clinical practice in the late 1980s. Lanreotide, another somatostatin analogue, became available in the mid-1990s initially as a prolonged-release formulation administered every 10 or 14 days. Long-acting release formulations of both octreotide (Sandostatin LAR and Novartis) and lanreotide (Somatuline Autogel, Ipsen), based on microparticle and nanoparticle drug-delivery technologies, respectively, were later developed, which allowed for once-monthly administration and improved convenience. First-generation somatostatin analogues remain one of the cornerstones of medical therapy in the management of pituitary and GEP-NET hormone hypersecretion, with octreotide having the longest established efficacy and safety profile of the somatostatin analogue class. More recently, pasireotide (Signifor), a next-generation multireceptor-targeted somatostatin analogue, has emerged as an alternative therapeutic option for the treatment of acromegaly. This review summarizes the development and clinical success of somatostatin analogues.

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Introduction

Somatostatin analogues are the current mainstay treatment for acromegaly and gastroenteropancreatic neuroendocrine tumours (GEP-NET).

Acromegaly: background

Acromegaly is a chronic metabolic disorder with an estimated prevalence of 40–125 cases per million and an annual incidence of three to four new patients per million (Katznelson et al. 2011). It affects both genders equally and generally develops between the fourth and fifth decades of life, although it may occur at any age (Katznelson et al. 2011). In most cases, acromegaly is caused by the presence of a benign tumour in the pituitary gland (Sanno et al. 2003), which secretes excess growth hormone (GH) with a concomitant increase in insulin-like growth factor 1 (IGF-1) by the liver, resulting in a proliferation of bone, cartilage and soft tissue. As the onset of physical changes is insidious, diagnosis can be delayed for up to 10 years in some patients (Rajasoorya et al. 1994), leading to potentially serious deleterious consequences for the patient's health and well-being. Most patients typically present at advanced stages with enlargement of the extremities and modification of facial features (Drange et al. 2000). Prolonged hypersecretion of GH and IGF-1 results in multiple significant co-morbidities, including cardiovascular complications (Powlson & Gurnell 2016), impaired glucose tolerance and diabetes (Biering et al. 2000, Kasayama et al. 2000), hypertension (Lombardi et al. 2006), respiratory conditions (Attal & Chanson 2010, Powlson & Gurnell 2016) and colorectal neoplasms (Rokkas et al. 2008). Symptoms related to these co-morbidities are the most likely reason for undiagnosed patients with acromegaly to seek medical attention (Katznelson et al. 2011). Mortality rate is increased in acromegaly, with standardized mortality ratios relative to the general population ranging from 1.3 to 1.9 (Dekkers et al. 2008, Ritvonen et al. 2015, Dal et al. 2016), which is further elevated if co-morbidities, particularly cardiovascular disease, are present (Sherlock et al. 2010). The clinical burden of acromegaly is further compounded by the substantial impairment in quality of life (QoL) (Rowles et al. 2005, Trepp et al. 2005, T'Sjoen et al. 2007). Additionally, patients with acromegaly may experience neurocognitive (Leon-Carrion et al. 2010, Martin-Rodriguez et al. 2013) and neuropsychiatric dysfunctions (Sievers et al. 2009a,b).

Prompt diagnosis and treatment are critical as longer duration of untreated or uncontrolled acromegaly is associated with more severe complications (Martin-Rodriguez et al. 2013). Indeed, in some patients, cognitive (Martin-Rodriguez et al. 2013) and psychosocial (Biermasz et al. 2004, van der Klaauw et al. 2008) impairment may be irreversible. Despite the urgency to diagnose and treat, many patients with acromegaly still have uncontrolled disease, and there may be many more undiagnosed (Katznelson et al. 2011).

GEP-NET: background

GEP-NETs are relatively rare neoplasms that may present with a diverse range of functional and behavioural characteristics (Oberg 2005). Endocrine tumours of the gastrointestinal tract have historically been classified as carcinoids of the foregut, midgut and hindgut, depending on anatomical origin, with midgut carcinoids constituting the largest group of GEP-NET (Robertson et al. 2006). The World Health Organization (WHO) uses different classifications that include well-differentiated and poorly differentiated GEP-NET. The former category of tumour is relatively slow growing, whereas the latter may present as a more aggressive malignancy (Solcia et al. 2000). Non-functioning endocrine tumours do not secrete measurable amounts of biologically active hormones; in contrast, hormone hypersecretion from functioning GEP-NET is responsible for causing distinct clinical syndromes. Carcinoid syndrome is characterized by a set of symptoms that include mild-to-severe diarrhoea, flushing of the face and wheezing attacks. Despite a dearth of curative treatment options for patients with GEP-NET, QoL for these patients has dramatically improved since the introduction of somatostatin analogue therapy, which effectively alleviates symptoms and potentially inhibits tumour progression.

This article summarizes the literature regarding the development and clinical impact of the first-generation somatostatin analogues octreotide and lanreotide, and introduces pasireotide as a next-generation somatostatin analogue, in the treatment of acromegaly and GEP-NET.

Clinical development

Originally discovered as an inhibitor of GH release (Brazeau et al. 1973), somatostatin is a peptide hormone that plays an inhibitory role in the regulation of multiple physiological functions, including pituitary, pancreatic and gastrointestinal hormone secretion.

Somatostatin exerts its biological effects by interaction with specific somatostatin receptors (SSTR) expressed on target tissues. Five human receptor subtypes have been recognized (SSTR1–5), each mediating a distinct signalling pathway (Patel 1999). GH-secreting pituitary tumours predominantly express SSTR2 and SSTR5 (Melmed 2006), whereas SSTR2 predominates in endocrine pancreatic tumours and carcinoids (de Herder *et al*. 2003).

Given its role in inhibiting such a diverse array of physiological processes, therapeutic exploitation of somatostatin for the treatment of endocrine-related disorders was quickly explored but ultimately abandoned because of its rapid degradation in human plasma. Octreotide was the first biologically stable somatostatin analogue to be synthesized (Fig. 1) that exhibited a longer half-life than native somatostatin (1.5–1.9 h vs 3 min) (Bauer *et al*. 1982), binding with high, low and moderate affinity to SSTR2, SSTR3 and SSTR5, respectively (Hofland & Lamberts 2003). It is also a more potent inhibitor of GH and insulin than somatostatin (Bauer *et al*. 1982). In patients with acromegaly, octreotide induced long-acting suppression of GH secretion without the rebound hypersecretion observed after somatostatin infusion (Lamberts *et al*. 1985*a*).

A short-acting immediate-release (IR) formulation of octreotide, administered either subcutaneously or intravenously, initially received regulatory approval for the treatment of acromegaly in Europe in 1988 (Fig. 1). Data from studies around this time (Lamberts *et al*. 1985*b*, Vance & Harris 1991, Ezzat *et al*. 1992) demonstrated the efficacy of octreotide IR in reducing GH and IGF-1 levels in patients with acromegaly. A long-acting formulation (octreotide long-acting repeatable) was introduced and later approved in 1995; octreotide LAR is a depot preparation of octreotide encapsulated within microspheres composed of a biodegradable polymer and administered by monthly intramuscular injection.

After a single injection of octreotide LAR, octreotide is released in a short burst to an initial peak within 1 h of administration, which then progressively decays within 12 h. A second-release phase then occurs, which exhibits sustained-release behaviour, reaching a plateau between days 14 and 42 (Lancranjan *et al*. 1995). Steady-state octreotide serum concentrations were reached after three injections and were 1.6-fold higher relative to plateau octreotide levels after the first injection (Lancranjan *et al*. 1995). In patients with acromegaly, the efficacy profile of octreotide LAR was found to be similar to that of octreotide IR, but with the added convenience of once-monthly administration (McKeage *et al*. 2003). Octreotide LAR is the most commonly prescribed formulation today, with octreotide IR primarily used in cases of symptom breakthrough or in perioperative situations.

Lanreotide is another metabolically stable somatostatin analogue that has demonstrated a similar binding profile to that of octreotide (Hofland & Lamberts 2003). The original sustained-release formulation (lanreotide SR) used a microparticle-based drug-delivery system, which was later followed by lanreotide Autogel, the first available sustained-release formulation based on self-assembling nanotube technology (Fig. 1) (Pouget *et al*. 2010). After administration, lanreotide peptide monomers are slowly released from the ends of the nanotubes over a period of 1 month. Lanreotide Autogel is available in prefilled syringes and is administrated by deep subcutaneous (sc) injection (Caron *et al*. 2002). Lanreotide Autogel has a different release pattern than that of octreotide LAR and is characterized by an initially sharp increase that generally reaches peak concentration on day 1, followed by a consistent decrease throughout the treatment period (Astruc *et al*. 2005).

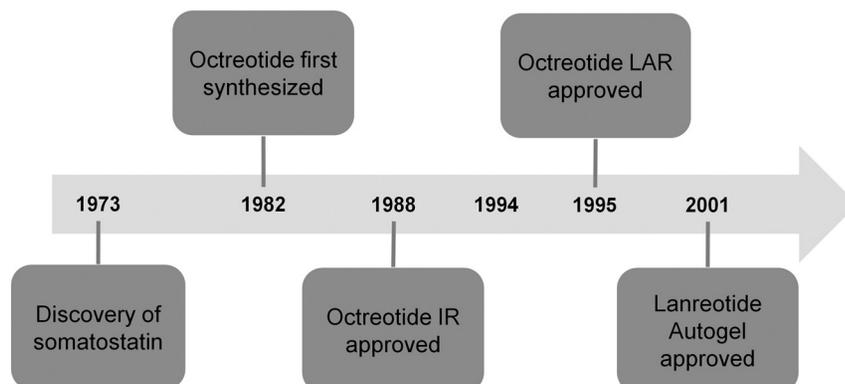Pasireotide is a next-generation, multireceptor-targeted somatostatin analogue with high affinity for

Figure 1
Development and regulatory approval timeline. Figure shows European regulatory approval for the treatment of acromegaly.

SSTR1–3 and SSTR5 (Schmid 2008). Binding affinity to SSTR5 is 39-fold higher than that of octreotide (Schmid & Schoeffter 2004). Two formulations of pasireotide have been developed: one for sc administration and another long-acting formulation (pasireotide LAR) for intramuscular injection (Fig. 1). Pasireotide administered subcutaneously to healthy volunteers was rapidly absorbed, with maximum plasma concentrations reached in less than 1 h (Petersenn et al. 2012a,b). Pasireotide LAR in healthy volunteers exhibited an extended-release profile characterized by an initial burst release, with plasma concentrations subsequently declining and then rising to a peak over approximately 1 week and 3 weeks, respectively (Dietrich et al. 2012).

Clinical experience: acromegaly

The 2014 Endocrine Society guidelines for the diagnosis and treatment of acromegaly defines a number of treatment goals: reducing circulating levels of GH and IGF-1, tumour volume reduction, improvement in symptoms and co-morbidities and reduction of mortality risk (Katznelson et al. 2014). Transsphenoidal surgery is the favoured approach in eligible patients, with remission rates of up to 90% and 50% in those with a microadenoma and macroadenoma, respectively (Nomikos et al. 2005, Trepp et al. 2005). Moreover, improved operative outcomes are associated with increasing neurosurgical experience (Ahmed et al. 1999, Gittoes et al. 1999). Patients with large adenomas (>20 mm) and a GH level >50 µg/L before surgery, however, are still likely to require medical therapy and possibly radiotherapy to control excess GH (Shimon et al. 2001, Nomikos et al. 2005). For patients who cannot have surgery, do not achieve remission either shortly after surgery or during long-term follow-up or experience disease recurrence after initial remission, medical therapy is indicated.

Suppression of excess GH and IGF-1 levels

Before the availability of somatostatin analogues, therapeutic options for patients with acromegaly were limited, with patients remaining uncontrolled for years (Kleinberg 2005). The introduction of octreotide in the 1980s was a quantum leap for medical therapy in acromegaly. In a meta-analysis by Freda and coworkers examining clinical trials of first-generation somatostatin analogues published before 2004, overall response rates to octreotide LAR and lanreotide SR, respectively, were 57 and 48% in terms of GH control, and 67 and 47% in terms of

normalization of IGF-1 (Freda et al. 2005). These findings were corroborated by two later analyses that reported generally similar response rates for both octreotide LAR and lanreotide Autogel (Murray & Melmed 2008, Colao et al. 2011). Together, these analyses have created the expectation that at least half of patients receiving somatostatin analogues should achieve biochemical control. However, there is considerable variation in reported biochemical response rates that is not evident from these reports. In a recent critical review of clinical trials that evaluated patients with acromegaly treated with first-generation somatostatin analogues from 1990 to March 2015, biochemical response rates ranged from 17 to 86% for octreotide LAR and 17 to 84% for lanreotide Autogel (Colao et al. 2016). Accounting for such disparity is complicated by multiple confounding variables that preclude direct comparisons between different studies. Although target threshold levels of biochemical control in the included studies are generally similar (ie, GH ≤2.5 µg/L and/or normalization of IGF-1), lack of standardization of GH and IGF-1 assays, different patient populations, inclusion or exclusion of treatment non-responders, use of composite endpoints (both mean GH and IGF-1 levels) and pre-treatment with medical therapy represent some of the key factors that can introduce bias into response rate reporting (Colao et al. 2016). Interestingly, in prospective studies using stringent composite measures of biochemical control to evaluate medical-treatment-naïve patients not pre-selected for responsiveness to prior somatostatin therapy, response rates are consistent, ranging from 17 to 37% (Colao et al. 2016).

In the largest prospective, randomized, active-controlled trial in medically naïve patients with acromegaly to date, pasireotide LAR was more effective at providing biochemical control (GH <2.5 µg/L and normal IGF-1) than octreotide LAR (31.3% vs 19.2%, respectively) after 1 year of treatment (Colao et al. 2014). Pasireotide LAR had a similar safety profile as that of octreotide LAR, except for a higher frequency and degree of hyperglycaemia.

Clinical utility as first-line therapy

Removing or reducing the size of the tumour is another guidelines-recommended goal of treatment, with neurosurgery being the accepted first-line treatment. However, pre-operative medical treatment may achieve better post-operative outcomes, as tumour shrinkage (Sheppard 2003, Melmed et al. 2005), and softening of the tumour parenchyma (Stevenaert & Beckers 1996, Abe & Ludecke 2001) induced by somatostatin analogues likely

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facilitates surgical resection. Octreotide LAR was shown in a recent meta-analysis to reduce tumour volume by 66.0% (95% confidence interval (CI), 57.0–74.0) (Giustina *et al.* 2012). Tumour volume reduction is typically observable within 3 months of initiating therapy and lasts for up to 4 years in some patients (Lundin *et al.* 1997, Melmed *et al.* 2005), although tumour regrowth may occur upon discontinuation of medical treatment (van der Lely *et al.* 2001*b*). The effect of primary lanreotide Autogel (120 mg) treatment on tumour size in treatment-naïve patients with GH-secreting macroadenomas was specifically assessed in the recent PRIMARYS study (Caron *et al.* 2014). In the intention-to-treat population, 62.9% (95% CI: 52.0–72.9) of 89 patients achieved clinically significant (≥20%) tumour volume reduction at 48 weeks or last follow-up. However, because the lower confidence limit was below a predetermined threshold of 55%, the study did not achieve its primary endpoint.

In a multicentre study, surgical remission (IGF-1 ≤ age-adjusted upper limit of normal (ULN)) at 3 months after surgery was achieved in half of newly diagnosed patients with macroadenomas who had received 6 months of pre-surgical treatment with octreotide LAR vs 16% who underwent surgery without pre-treatment (Carlsen *et al.* 2008). Long-term observational data (1 and 5 years post-operatively) for these patients, however, revealed no significant impact of pre-operative treatment on macroadenomas (Fougner *et al.* 2014). Remission rates (IGF-1 ≤ age-adjusted ULN) of 49 and 18% were found in a single-centre study of 98 patients with newly diagnosed macroadenomas who received 4-month pre-treatment with lanreotide Autogel before surgery or surgery without pre-treatment, respectively (Mao *et al.* 2010). Shen and coworkers reported that pre-surgical treatment of invasive macroadenomas with octreotide LAR increased total resection rates and short-term remission rates (both GH and IGF-1 normalized) vs no pre-treatment; however, remission rates during long-term follow-up of the pre-treated group showed no advantage (Shen *et al.* 2010). A retrospective analysis of 286 patients revealed that surgical remission rates were not significantly different whether octreotide or lanreotide was given pre-operatively or not (Losa *et al.* 2006). A recent meta-analysis suggested a statistically significant effect of pre-operative medical therapy on surgical outcome when three prospective controlled trials were analysed, with a pooled odds ratio for biochemical cure with somatostatin analogue pre-treatment of 3.62 (95% CI: 1.88–6.96) (Pita-Gutierrez *et al.* 2013). It should be noted, however, that the beneficial effect of pre-treatment was demonstrated only in centres

with low rates of cure with primary surgical treatment. Given the existing evidence, current guidelines do not advocate the routine use of pre-operative medical therapy (Katznelson *et al.* 2014).

Improvements in symptoms, co-morbidities and reductions in excess mortality risk

In addition to preventing continued tumour growth, medical therapy of pituitary tumours also provides marked relief of symptoms in up to 70% of patients with acromegaly. Reduced episodes of headache, fatigue, joint pain, carpal tunnel syndrome and perspiration with octreotide treatment have been noted (Vance & Harris 1991, Ezzat *et al.* 1992, Newman *et al.* 1995). Disease-associated co-morbidities, including cardiac and respiratory disorders, also improve with somatostatin analogue therapy (Colao *et al.* 2008). This is particularly important given that cardiovascular co-morbidities serve as the major events that limit patient survival. Crucially, early diagnosis and normalization of GH or IGF-1 levels have been shown to ameliorate the excess mortality risk associated with acromegaly (Swearingen *et al.* 1998, Holdaway *et al.* 2008). Given that up to 40% of patients with acromegaly may show discordant GH and IGF-1 levels (Alexopoulou *et al.* 2008), achieving target levels of both biochemical measures is a better indicator of attaining a life expectancy equivalent to that of the general population (Holdaway *et al.* 2008).

Therapeutic options for biochemically uncontrolled patients

Despite the clinical success of somatostatin analogue therapy in the treatment of acromegaly, up to half of patients may be biochemically uncontrolled (Freda *et al.* 2005, Murray & Melmed 2008, Colao *et al.* 2011, Carmichael *et al.* 2014). Although the reasons for not achieving biochemical control with somatostatin analogues are not fully elucidated, the phenomenon appears to be multifactorial, involving both clinical characteristics and molecular-based mechanisms (Gadelha *et al.* 2013). With respect to the latter, high tumour expression levels of SSTR2 generally predicts a successful response, whereas patients with low-SSTR2-expressing tumours exhibit resistance and have a correspondingly poorer response (Taboada *et al.* 2008, Gatto *et al.* 2013, Wildemberg *et al.* 2013). Interestingly, some patients with high-SSTR2-expressing tumours may also exhibit resistance (Kasuki *et al.* 2012).

Clinical practice guidelines recommend assessing the efficacy of somatostatin analogue therapy after 3 months (Katznelson *et al*. 2014). In those patients who do not achieve adequate symptom or biochemical control with the starting dose of octreotide LAR, flexibility exists either to up-titrate or to decrease the dosing interval (Giustina *et al*. 2009, 2014, Fleseriu 2011, Mazziotti *et al*. 2011) (Fig. 2). Conversely, for patients who have achieved biochemical control with chronic octreotide LAR therapy, dosage can be reduced or the interval between doses can be extended beyond the recommended 4 weeks without compromising GH and IGF-1 levels or clinical response (Jenkins *et al*. 2000, Biermasz *et al*. 2003, Turner *et al*. 2004). For well-controlled patients receiving lanreotide Autogel 60 or 90 mg, the US Food and Drug Administration (FDA) has approved an extended dosing interval from 4 weeks to 6–8 weeks with an increase in the dose of lanreotide Autogel to 120 mg.

Withdrawal of chronic somatostatin analogue therapy is only a realistic option in those rare patients with persistent optimum control on relatively low doses administered at long intervals (Ramirez *et al*. 2012).

For patients partially controlled or uncontrolled on first-generation somatostatin analogue therapy, a number of therapeutic options are available, including monotherapy with either pasireotide LAR or the GH receptor antagonist pegvisomant. In the 24-week, Phase III PAOLA trial of 198 patients uncontrolled (mean GH $\geq 2.5\,\mu$g/L and IGF-1 $> 1.3 \times$ ULN) on octreotide LAR or lanreotide Autogel treatment, patients were randomized to pasireotide LAR 40 mg ($n = 65$), pasireotide LAR 60 mg ($n = 65$) or continued treatment with octreotide LAR 30 mg or lanreotide Autogel 120 mg (active control group; $n = 68$). Pasireotide LAR 40 and 60 mg provided biochemical control in 15% ($P = 0.0006$ vs active control) and 20% ($P < 0.0001$ vs active control) of patients, respectively, compared with no patients in the control group (Gadelha *et al*. 2014). Pasireotide LAR had a similar safety profile as that of first-generation somatostatin analogues, except for a higher frequency and degree of hyperglycaemia.

In early registration trials of pegvisomant in patients with acromegaly, treatment resulted in normalization of IGF-1 in 82–97% of patients (Trainer *et al*. 2000, van der Lely *et al*. 2001*a*). Subsequent studies have reported lower rates of IGF-1 normalization of 51–78% (Barkan *et al*. 2005, Schreiber *et al*. 2007, Ghigo *et al*. 2009, Trainer *et al*. 2009). In the global observational ACROSTUDY of 1288 patients with acromegaly receiving pegvisomant, 63.2% of patients had normal IGF-1 levels after 5 years of pegvisomant treatment (van der Lely *et al*. 2012). Pegvisomant has been generally well tolerated to date (Trainer *et al*. 2000, 2009, van der Lely *et al*. 2001*a*, Barkan *et al*. 2005, Schreiber *et al*. 2007, Ghigo *et al*. 2009), although regular monitoring of hepatic function and serial magnetic resonance imaging to evaluate tumour size are recommended (Katznelson *et al*. 2014).
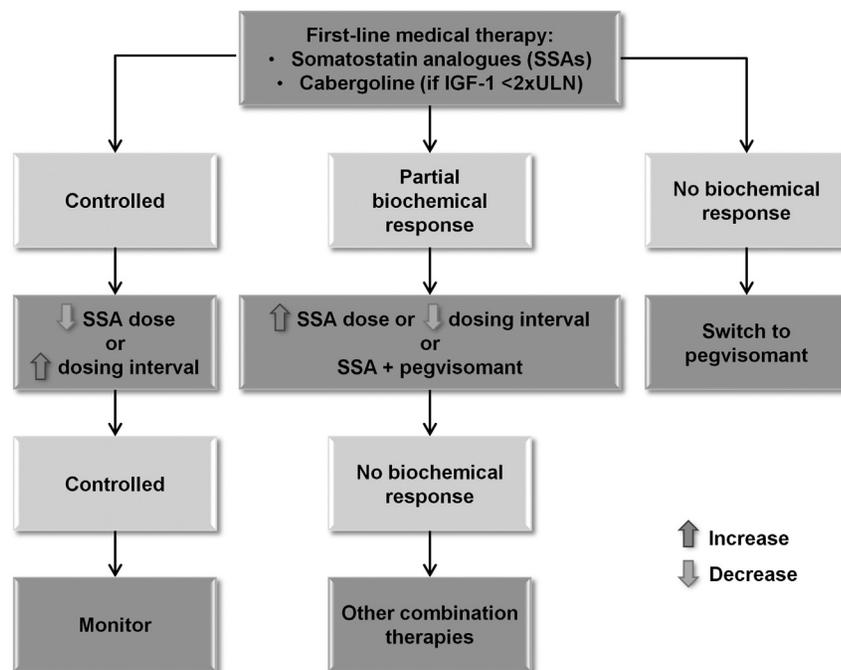

Figure 2

Algorithm for the approach to medical therapy in patients with acromegaly. Reproduced, with permission, from Giustina A, Chanson P, Kleinberg D, Bronstein MD, Clemmons DR, Klibanski A, van der Lely AJ, Strasburger CJ, Lamberts SW, Ho KKY, *et al*. (2014) Expert consensus document: a consensus on the medical treatment of acromegaly, *Nature Reviews Endocrinology*, volume 10, issue 4, pages 243–248. Copyright 2014, Rights Managed by Nature Publishing Group.

Combination therapy may also be considered in patients exhibiting partial responses to first-generation somatostatin analogues despite dose adjustments (Fig. 2). Sandret and coworkers systematically reviewed all trials of the dopamine receptor agonist cabergoline for the treatment of acromegaly and found that cabergoline in combination with a somatostatin analogue normalized IGF-1 levels in approximately half of patients previously uncontrolled on somatostatin analogue therapy (Sandret *et al.* 2011). However, the effect of cabergoline was found to be dependent on the baseline IGF-1 level, with the best response being observed in patients with IGF-1 levels <2×ULN.

In a single-centre study of 141 patients with acromegaly and persistently elevated IGF-1 levels (>1.2×ULN) despite at least 6 months of somatostatin analogue therapy, treatment with pegvisomant in combination with somatostatin analogues (median treatment duration, 4.9 years) improved control of IGF-1 in 97.0% of patients (Neggers *et al.* 2014). Combination therapy was well tolerated, similarly as what has been observed with pegvisomant monotherapy.

In patients uncontrolled on primary somatostatin analogue therapy, tumour debulking has been shown to improve subsequent responses to first-generation somatostatin analogues (Petrossians *et al.* 2005) and thus may be a therapeutic option for some patients.

Disease management considerations

Cost effectiveness is an increasingly important consideration in management decisions in acromegaly (Ben-Shlomo *et al.* 2011). Although treatment costs are substantial, they are not significantly higher than those associated with other chronic diseases (Katznelson *et al.* 2011). However, as the cost effectiveness of medical therapies for acromegaly has not been comprehensively evaluated, more careful studies are required to better determine the cost/benefit ratio. The impact of chronic therapy on QoL is also a key consideration. Acromegaly is associated with substantially reduced QoL (Rowles *et al.* 2005, Kauppinen-Makelin *et al.* 2006, Webb 2006), in a similar manner as osteoarthritis (Rowles *et al.* 2005), whereas obese patients report better QoL scores in terms of appearance and general health (Rowles *et al.* 2005, Webb 2006). Improvements in biochemical control provided by octreotide LAR and lanreotide Autogel have been found to parallel improvements in QoL (Matta *et al.* 2008, Mangupli *et al.* 2014, Caron *et al.* 2016).

Clinical experience: GEP-NET

Radical surgery is the only 'curative' treatment for GEP-NET; however, with more than half of tumours being unresectable at diagnosis (Kim *et al.* 2010), symptoms caused by tumour-related hormone hypersecretion are managed with somatostatin analogue therapy. Short-acting octreotide was the first biotherapeutic agent used for the successful control of symptoms associated with carcinoid tumours, but it requires long-term administration of multiple daily injections. A randomized, double-blind study by Rubin and coworkers first demonstrated that octreotide LAR had similar efficacy to the short-acting formulation in the treatment of carcinoid syndrome once steady-state octreotide concentrations were achieved (Rubin *et al.* 1999). Octreotide LAR has since removed the need for daily injections, although breakthrough symptoms may still require treatment with its short-acting formulation. Pooled data from studies of octreotide in GEP-NET conducted between 1986 and 2004 indicate that up to 70% of patients experience resolution of diarrhoea or flushing with octreotide treatment (Modlin *et al.* 2006). Lanreotide has also shown comparable efficacy with octreotide in improving flushes and diarrhoea in patients with carcinoid syndrome, providing relief of symptoms in up to 80% of patients (Modlin *et al.* 2006).

Antitumour effect

Although somatostatin analogues have long been indicated for symptom relief associated with GEP-NET, there is a growing body of evidence to indicate associated antitumour activity. Although treatment for GEP-NET is multimodal, it has been speculated that the introduction of octreotide in 1987 and its subsequent clinical use has contributed to improved patient survival (Halfdanarson *et al.* 2008, Yao *et al.* 2008). Two analyses of the Surveillance, Epidemiology and End Results (SEER) database revealed a marked improvement in survival duration of patients with GEP-NET between 1988 and 2004 compared with patients diagnosed earlier (Yao *et al.* 2008), as well as an increase in survival of patients with pancreatic NET over the period 1973–2000 (Halfdanarson *et al.* 2008). In support of these findings, a review of 90 patients with carcinoid syndrome treated during the somatostatin analogue era had 5-year survival rates of 67% compared with 18% for historical controls (Anthony *et al.* 1996).

The antitumour effect of octreotide in clinical studies of patients with GEP-NET has been evaluated

in two reviews. Eriksson and Oberg found that, in studies of octreotide spanning its introduction up to the late 1990s, approximately half of the patients with GEP-NET achieved stabilization of tumour growth (i.e., no increase or decrease in tumour size), with 10–20% showing tumour regression (Eriksson & Oberg 1999). A more recent review that analysed trials conducted between 1987 and 2011 revealed that stable disease in patients with poorly differentiated, functioning or non-functioning GEP-NET was achieved in up to 86% treated with octreotide sc and up to 88% in those receiving octreotide LAR (Sideris *et al.* 2012). Partial tumour response (i.e., a predefined reduction in overall tumour load) reached 31 and 11% for octreotide sc and octreotide LAR, respectively, broadly in agreement with the earlier findings by Eriksson and Oberg (Eriksson & Oberg 1999). Partial response and stable disease rates for lanreotide are similar to those reported for octreotide (up to 31 and 78%, respectively). Lanreotide Autogel has been less well studied than octreotide LAR in the treatment of GEP-NET. In one study in patients with well-differentiated GEP-NET, stable disease and partial tumour response were reported in 89 and 4% of patients, respectively (Martin-Richard *et al.* 2011).

PROMID was the first large trial to confirm the antitumour effect of octreotide LAR in a randomized setting (Rinke *et al.* 2009). In 85 treatment-naïve patients with well-differentiated metastatic GEP-NET of the midgut, median time to tumour progression was significantly extended with octreotide LAR (14.3 months (95% CI: 11.0–28.8)) compared with placebo (6 months (95% CI: 3.7–9.4)); stable disease was observed in 67 and 37% of patients treated with octreotide LAR and placebo, respectively. The antitumour response was more pronounced in patients with a hepatic tumour burden of ≤10%. Notably, no differences in response were reported between functioning and non-functioning GEP-NET. Median survival time for both treatment groups could not be reliably determined. It is currently unclear as to whether octreotide therapy confers improved overall survival in patients with GEP-NET of the midgut. Despite some reservations concerning aspects of the study design (Yao *et al.* 2013), data from PROMID were significant enough to prompt updates to several treatment guidelines to recommend 20–30 mg of octreotide LAR in patients with recurrent or unresectable GEP-NET (Anthony *et al.* 2010, Boudreaux *et al.* 2010, Kulke *et al.* 2011, Oberg *et al.* 2012). A treatment algorithm is shown in Fig. 3.

The Lanreotide Antiproliferative Response in Patients with GEP-NET (CLARINET) trial represents only the second Phase III randomized study to confirm the antitumour effect of somatostatin analogues. In this 96-week study, 204 medically naïve patients with well-differentiated or moderately differentiated non-functioning GEP-NET were randomized to receive either lanreotide Autogel 120 mg or placebo. The primary endpoint of PFS was met, with lanreotide Autogel demonstrating superiority to placebo in prolonging PFS compared with placebo: median PFS was not reached with lanreotide Autogel vs 18 months with placebo (hazard ratio 0.47; 95% CI: 0.30–0.73; *P* < 0.001). After 2 years of treatment, estimated rates of PFS were 65.1 and 33.0% in the lanreotide Autogel and placebo groups, respectively (Caplin *et al.* 2014).

Several key differences between the PROMID and CLARINET studies likely account for the longer PFS observed in the latter study. First, the patient population in the CLARINET study was more heterogeneous than that in the PROMID study, with 96% of patients exhibiting no disease progression 3–6 months before study randomization (Caplin *et al.* 2014). It is possible that tumours in patients who participated in the CLARINET trial were potentially less aggressive than those in PROMID. Secondly, the studies used different criteria for progression: the WHO criterion used in PROMID was a 25% increase in the product of tumour bi-dimensional diameters, which corresponds to a 44% increase according to the Response Evaluation Criteria in Solid Tumors (RECIST) used in CLARINET (Strosberg *et al.* 2015). Thus, PFS in PROMID would likely have been longer if it was assessed using RECIST criteria.

The molecular basis of the antiproliferative effect of octreotide in GEP-NET is largely unknown. Research conducted in cultured cells derived from tumours other than GEP-NET suggests that the octreotide–SSTR2 interaction is coupled to proliferative signalling pathways that directly or indirectly modulate cell cycling (Pagès *et al.* 1999), apoptosis (Ferrante *et al.* 2006) and angiogenesis (García de la Torre *et al.* 2002). Angiogenesis (in particular, the phosphoinositide 3-kinase/Akt/ mammalian target of rapamycin (mTOR) pathway) has been clinically validated as a therapeutic target following the finding that everolimus, an mTOR inhibitor, improved progression-free survival (PFS) compared with placebo in patients with well-differentiated pancreatic NET (Yao *et al.* 2011). A synergistic drug combination approach that exploits more than one mechanism of action has been shown to enhance antitumour activity in patients with GEP-NET. The randomized,
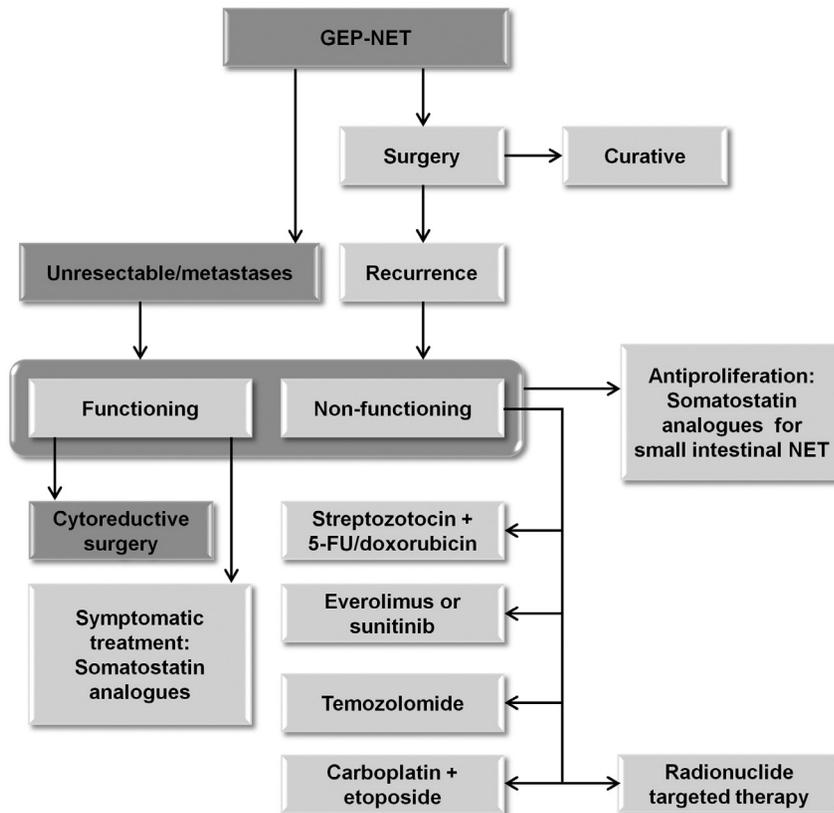
Figure 3
Algorithm for the treatment of GEP-NET. Adapted, with permission, from Oberg K, Knigge U, Kwekkeboom D & Perren A, Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, *Annals of Oncology*, 2012, volume 23 (Supplement 7), pages vii124–vii130, by permission of Oxford University Press.

double-blind, placebo-controlled, Phase III RAD001 in Advanced Neuroendocrine Tumors (RADIANT-2) study evaluated everolimus in combination with octreotide LAR in patients with low- or intermediate-grade advanced NET (Pavel *et al.* 2011). Patients treated with everolimus plus octreotide LAR were more likely to experience tumour volume reduction than patients receiving placebo plus octreotide LAR (75% vs 45%, respectively). This combination led to a clinically meaningful 5.1-month improvement in PFS vs placebo plus octreotide LAR (16.4 vs 11.3 months). Concerns were expressed, however, that the patient population enrolled in RADIANT-2 was not as defined as that for PROMID, with diversity of tumours causing baseline imbalances that potentially affected outcomes (Yao *et al.* 2013).

Safety and tolerability

With two and a half decades of clinical experience, octreotide has a well-established safety profile. Adverse events associated with lanreotide are generally similar to those seen with octreotide. Gastrointestinal-related complaints are the most frequently reported side effects, being mild to moderate in severity and attributable to drug-induced disruption of GEP hormone signalling and

reduced secretion of digestive enzymes (Bornschein *et al.* 2009). Altered secretion of cholecystokinin can lead to abnormalities in the biliary system (Moschetta *et al.* 2001). Up to one-third of patients with acromegaly may develop biliary sediment/sludge, microlithiasis or gallstones (Catnach *et al.* 1993, Lamberts *et al.* 1996, Attanasio *et al.* 2003, Plöckinger *et al.* 2008), whereas almost half of patients with advanced GEP-NET are at risk of developing gallstones and/or biliary sludge while receiving chronic first-generation somatostatin analogue therapy (Trendle *et al.* 1997).

In patients with acromegaly treated with octreotide, prolongation of the QT interval on electrocardiogram (ECG) has been observed with clinical symptoms of bradycardia (Novartis Pharmaceuticals 2012). Lanreotide-induced bradycardia is currently limited to one case report (Ogmen *et al.* 2015). It should be noted that untreated patients with acromegaly display ECG abnormalities: in a retrospective study of 30 patients with acromegaly, mean baseline QT interval corrected for heart rate (QTc) was significantly longer in patients than in healthy volunteer controls (438.6 ± 4.83 ms vs 407.9 ± 5.86 ms, $P < 0.001$) (Fatti *et al.* 2006). Moreover, in a subset of patients ($n = 24$) treated with long-term somatostatin analogue therapy, QTc decreased significantly in

patients to mean levels comparable with controls (from 436.5 ± 4.89 ms to 421.0 ± 6.06 ms, $P < 0.001$).

First-generation somatostatin analogues have the potential to alter glucose homeostasis, although individual responses in terms of glucose tolerance vary widely (Ronchi et al. 2002, Baldelli et al. 2003). In a prospective, non-randomized, 5-year study of 100 patients treated with surgery, somatostatin analogues or both (in a crossover design), a decrease in fasting glucose levels occurred only in those patients treated with medical therapy alone (Colao et al. 2009). However, a meta-analysis by Mazziotti and coworkers could not confirm an influence of somatostatin analogues on fasting glucose levels (Mazziotti et al. 2009). Patients with diabetes mellitus are, nevertheless, recommended to control their blood sugar levels strictly.

Pasireotide has a similar safety profile as that of first-generation somatostatin analogues, except for a higher frequency and degree of hyperglycaemia (Colao et al. 2012, 2014, Gadelha et al. 2014). Increases in blood glucose levels associated with pasireotide treatment are attributable to its receptor-binding profile (Bruns et al. 2002, Schmid & Brueggen 2012). At present, it is unclear how the deterioration in glucose metabolism fits with the improved GH/IGF-1 levels.

The shape of things to come

Oral octreotide

In a recent Phase III trial, 98/151 (65%) patients with acromegaly, previously controlled with somatostatin analogue therapy, maintained biochemical control (GH <2.5 ng/mL and IGF-1 < 1.3 × ULN) after being switched to an oral formulation of octreotide (Octreolin) for up to 7 months (Melmed et al. 2015). Fifteen percent and 11% of patients discontinued because of treatment failure (IGF-1 > 1.3 × ULN) and possible drug-related adverse events, respectively. There were two deaths reported: one from myocardial infarction and another from suspected biliary obstruction and sepsis. Although these findings are preliminary, the efficacy and safety profile of Octreolin are consistent with those of current injectable somatostatin analogue therapies and may potentially offer improved convenience.

Octreotide sc depot

Despite the established clinical credentials of octreotide LAR, this formulation requires a multistep reconstitution process and a requirement for intramuscular injection, both of which must be performed by health care professionals. Octreotide sc depot is a novel formulation of octreotide based on liquid–lipid-crystal technology (Tiberg & Johnsson 2011, Tiberg et al. 2012a,b) that permits the use of thin needles for sc injection with planned availability in prefilled syringes. In a Phase I pharmacokinetic (PK) and pharmacodynamic (PD) study, octreotide sc depot provided greater octreotide bio-availability, with more rapid onset and similar duration of PD effect (in terms of IGF-1 suppression), compared with octreotide LAR in healthy volunteers (Tiberg et al. 2015). The improved PK/PD profile and the practical advantages of the sc depot formulation over the currently marketed LAR formulation (including the potential for self-administration or partner administration) mark this novel drug-delivery technology as a significant advancement over the existing polymer-based system. Phase II and III studies will further evaluate octreotide sc depot in patients with acromegaly and GEP-NET.

Pasireotide LAR in GEP-NET

Pasireotide has demonstrated effective symptom control in patients with GEP-NET: in a Phase II, multicentre study of 44 patients with advanced GEP-NET whose symptoms were refractory or resistant to octreotide LAR, pasireotide treatment provided relief of symptoms (diarrhoea and flushing) in 27% of patients (Kvols et al. 2012). Additionally, in a Phase III study of pasireotide LAR vs high-dose (40 mg) octreotide LAR in 110 patients with advanced GEP-NET whose disease-related symptoms were uncontrolled by first-generation somatostatin analogues at maximum approved doses, pasireotide LAR and octreotide LAR had similar effects on symptom control (Wolin et al. 2015). These data warrant further investigation into the role of pasireotide LAR in the treatment of GEP-NET.

Peptide receptor radionuclide therapy in NET

The incorporation of somatostatin analogues into radiopharmaceuticals allows for targeted delivery of radiation to SSTR-expressing tumours. The efficacy of [177Lu]-DOTATATE (Lutathera), a conjugate consisting of octreotate radiolabelled with 177Lu, has been evaluated in patients with advanced midgut NET in the NETTER-1 Phase III study (Strosberg et al. 2016); 230 patients were randomized (1:1) to receive [177Lu]-DOTATATE and octreotide LAR 60 mg. Preliminary analysis

showed that, compared with high-dose octreotide LAR, fewer patients experienced disease progression with [177Lu]-DOTATATE (23 vs 64 patients, respectively), median PFS was extended (8 months vs not reached) and there were substantially fewer deaths (13 vs 22) (Strosberg *et al.* 2016). Longer follow-up will better determine the impact of [177Lu]-DOTATATE on overall survival. Peptide receptor radionuclide therapy may also use somatostatin-based conjugates radiolabelled with 90Y for internal radiotherapy after systemic application. Although 90Y has greater tissue penetration and a longer half-life than 177Lu (Kam *et al.* 2012), one study in patients with advanced NET showed no difference in median overall survival between the two radionuclides; however, renal toxicity was more evident with 90Y (Romer *et al.* 2014). Combination therapy with 90Y and 177Lu may be a more effective therapeutic approach than either radioisotope alone (Villard *et al.* 2012).

Conclusions

First-generation somatostatin analogues are efficacious in the treatment of acromegaly and symptom control in GEP-NET, with a favourable safety profile based on more than 25 years of clinical experience with octreotide. A growing body of clinical evidence supports the antitumour activity of somatostatin analogues, reducing tumour bulk in acromegaly and slowing tumour growth in GEP-NET. Whether this antitumour effect translates into a survival benefit will require further controlled trials in a larger number of patients with GEP-NET. Despite the impressive credentials, some patients with acromegaly remain uncontrolled with either octreotide or lanreotide therapy. Pasireotide is an effective alternative treatment option for some of these patients, although hyperglycaemia needs to be monitored and managed. First-generation somatostatin analogues continue to evolve with the development and introduction of new formulations that promise improved patient benefits.

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