Somatostatin analogues therapy in gastroenteropancreatic neuroendocrine tumours: current aspects and new perspectives

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Running title: Somatostatin analogues treatment in GEP-NET
Abstract

Gastroenteropancreatic neuroendocrine tumours (GEP NETs) are rare tumours that present many clinical features secreting peptides and neuroamines that cause distinct clinical syndromes such as carcinoid syndrome. However most of them are clinically silent until late presentation with mass effects. Surgical resection is the first line treatment for a patient with a GEP NET while in metastatic disease multiple therapeutic approaches are possible. GEP NETs are able to express somatostatin receptors (SSTRs) bounded by somatostatin (SST) or its synthetic analogues, although the subtypes and number of SSTRs expressed is very variable. In particular somatostatin analogues are used frequently to control hormone-related symptoms while their anti-neoplastic activity seems to result prevalently in tumour stabilisation. Patients who fail to respond or cease to respond to standard SST analogues treatment seem to have a response to higher doses of these drugs. For this reason the use of higher doses of somatostatin analogues will probably improve the clinical management of these patients.

INTRODUCTION

Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) are characterized by an yearly incidence of 1.2-3.0 cases/100,000 inhabitants [1-5]. The majority of the GEP-NETs are sporadic but they can be also part of familiar syndromes such as MEN 1 syndrome, von Hippel-Lindau disease and neurofibromatosis type 1 while the clinical characteristics depend on the site of the primary tumour and its ability to secrete neuroamines and peptides. Among functioning tumours, major clinical entities are represented by carcinoid syndrome, hypoglycaemic syndrome, Zollinger-Ellison syndrome, WDHA (Water Diarrhea-Hypo-kaliemia-Achlorydria) syndrome, glucagonoma syndrome. However most of the GEP NETs are not able to produce biologically active hormones (non functioning tumours) and therefore
the diagnosis is often made too late only for the presence of symptoms due to the mass effect and/or metastases, mainly hepatic [1]. In patients with localized well differentiated neuroendocrine carcinomas, 5-year survival is 60–100% while with regional disease or distant metastases 5-year survival is 40% and 29%, respectively [6]. Around 80% of GEP-NETs express somatostatin receptors (SSTRs); they are five different G-protein coupled receptor subtypes (SSTRs 1-5) that are differently expressed in the various types of tumour (Table 1 and 2). It is important to underline that SSTRs are present not only in neoplastic tissues. For example Beneyto and co-workers used in situ hybridization to quantify the mRNA expression levels of SST receptors subtype 1 (SSTR1) and subtype 2 (SSTR2) in dorsolateral prefrontal cortex area 9 from 23 matched pairs of subjects with schizophrenia and normal comparison subjects. SSTR1 mRNA levels did not differ between subject groups while mean cortical SSTR2 mRNA levels were significantly 19% lower in the subjects with schizophrenia [7]. Moreover in a very interesting and complete work, Pasquali and co-workers, reported that the radiolabeled somatostatin (SST) analog octreotide accumulates within the orbits of active Graves' ophthalmopathy (GO), and octreotide and lanreotide have been proposed to treat this disorder. In particular the authors described the expression of SST1-5 genes in lymphocytes recovered from retroorbital tissues obtained from patients with GO undergoing orbital decompression. All SSTs transcripts were found in lymphocytes both from GO retroorbital tissues and blood samples [8]. In addition, recent studies have shown that SSTRs are preferably expressed in well-differentiated neoplasia and some advanced forms loose particular receptor subtypes while keeping others [9, 10]; SSTRs subtypes can form homo/heterodimers at the membrane level, developing new receptors with different functional features [11], and that this receptor dimerization may be induced by addition of either dopamine or somatostatin (Fig. 1). In a study examining 81 functioning and non-functioning GEP-NETs the large part of the tumours expressed SSTRs 1, 2, 3 and 5, while SSTR 4 was detected only in a small minority [12]. SSTRs have been extensively mapped in different pancreatic tumours by means of autoradiography, reverse-transcription polymerase chain reaction, in situ hybridization and immunohistochemistry; SSTRs 1, 2, 3 and 5 are usually expressed in pancreatic NETs in particular insulinomas had
heterogeneous SSTRs expression while 100% of somatostatinomas expressed SSTR 5 and 100% of gastrinomas and glucagonomas expressed SSTR 2 [13]. Somatostatin (SST) is a natural peptide hormone secreted in various parts of the human body, including the digestive tract, able to inhibit the release of numerous endocrine hormones, including insulin, glucagon, and gastrin. The biological effects of somatostatin are mediated through its specific receptors (SSTRs 1–5) all bind natural peptides (somatostatin 14, somatostatin 28 and cortistatin) with similar high affinity. However, endogenous somatostatin short half-life in circulation (1–3 min), makes it difficult to use it continuously and has resulted in the development of synthetic analogues from the early 1980s when a number of short synthetic analogues of somatostatin including SMS201-995 (octreotide), RC-160 (vapreotide), BIM 23014 (lanreotide), and MK 678 (seglitide) were developed. These cyclic octapeptides are more resistant to peptidases and their half-lives and hence their biological activities are substantially longer than native somatostatin (1.5–2 h vs 1–2 min) [14]. Moreover, the development of a depot formulation of octreotide (octreotide long-acting repeatable - LAR), administered up to 30 mg once every 4 weeks has to a large extent eliminated the need for daily injections. Lanreotide SR (slow release) 30, 60 and 90 mg formulations administered every 10–14 days, has a similar efficacy to octreotide in the treatment of carcinoid tumors [15]. A new slow release depot preparation of lanreotide, Lanreotide Autogel, is administered subcutaneously up to 120 mg once a month [16]. Native SST and its synthetic analogues show different affinity for the five specific SSTRs [11, 12, 17]. Native SST binds all the five receptor subtypes (SSTRs 1-5). The effects of the SST analogues are mediated by the interaction with SSTR 2 and 5 receptors while the new somatostatin analogue, pasireotide (SOM 230), shows higher binding capacity towards SSTRs 1, 2, 3 and 5 with no agonist activity at the type 4 receptor [17] (Table 3). Moreover, in vitro studies demonstrated that SOM 230 was more effective than octreotide to control cell proliferation and apoptosis (Effects of somatostatin analog SOM230 on cell proliferation, apoptosis, and catecholamine levels in cultured pheochromocytoma cells [18]. The different receptor subtypes binding affinities seems to result in different biological and clinical activities [12].
The symptomatic and biochemical effects of SST analogues

GEP-NETs first line therapy, where possible, is always an aggressive surgical approach, aimed to obtain a curative tumour ablation, even in the presence of metastatic disease. However, in patients with functioning or metastatic tumours, the treatment goal is to improve their quality of life trying to alleviate the tumour associated symptoms and increasing survival [2, 14, 15]. Recently, the diagnostic and therapeutic approach of GEP NETs has considerably improved, mainly due to better imaging techniques (CT, MRI, PET) and somatostatin analogue-based imaging methods, as well as receptor subtype characterisation and the introduction of long-acting somatostatin analogues [19-25]. Usually, the treatment with long acting preparations of SST analogues consists in an intramuscular injection (i.m.) every 2 or 4 weeks (octreotide LAR, 10-30 mg; lanreotide autogel 60-120 mg) and the efficacy in the control of symptoms is well-documented [2,14,15], even if patients with islet cell tumour often show a transient (median time 2.5 months) and non-significant response [19-25]. The drugs are safe and well-tolerated in both long- and short-term treatments [26-30]. However, after 9-12 months, drug resistance should appear and patients may show symptoms of recrudescence. In such cases the approach proposed was to continue the treatment by increasing the analogue dosage or by shortening the administration range [31]. A randomised double-blind trial compared long-acting octreotide LAR at 10, 20, and 30 mg every 4 weeks with open-label short-acting octreotide every 8 h for the treatment of carcinoid syndrome. It showed that the efficacy of short-acting octreotide and of the long acting octreotide-LAR was the same once circulating octreotide steady-state concentrations were achieved [32]. O’Toole et al in a multicentre study on 33 patients with the carcinoid syndrome comparing the treatment with lanreotide (30 mg i.m. every 10 days) versus octreotide (200 μg s.c. twice or thrice daily) founded no significant differences in controlling symptoms (53.8% and 45.4%, respectively). Lanreotide and octreotide may also significantly lower the levels of the catabolite of serotonin (urinary 5-hydroxyindoleacetic acid / 5-HIAA), [33]. Ruszniewski et al evaluated the efficacy
and safety of the 28-day aqueous prolonged release formulation of lanreotide in 75 patients in a 6-month dose titration study where 30% of patients showed a biochemical response and 75% and 80% of patients reported resolution of diarrhea and flushing, respectively. The median decrease in levels of urinary 5-HIAA and serum chromogranin A was 24% and 38%, respectively [34]. An interim analysis of a phase II trial of SOM230 in 21 patients with metastatic carcinoid tumours whose symptoms (diarrhea and flushing) were refractory/resistant to octreotide LAR showed symptom relief in 33% [35]. Approximately 10–15% of patients with midgut carcinoids suffer from watery diarrhoea, flushing, right-sided heart failure and bronchial constriction (carcinoid syndrome), due to the tumour hypersecretion of a variety of endocrine substances, the most frequent of which are serotonin (5-hydroxytryptamine) and the tachykinins [36, 37], and therefore somatostatin analogues are important palliative tools for these patients. In insulinoma it has been noted that octreotide treatment may induce hypoglycemia worse in those patients lacking SSTRs 2 and 5, and, as glucagon secretion is also inhibited, patients have to be observed closely at the beginning of therapy to prevent severe hypoglycemia due to the reduced glucagon-dependent counter-regulation [38]. Hence, this treatment has to be started in a hospital setting, and should be reserved for only the minority of insulinoma patients with positive imaging on SRS. Vezzosi et al recently assessed that octreotide was effective in the control of hypoglycaemia in more than 50% of the insulinoma patients [39]. The treatment was effective in all SSTR 2 positive patients and in a few SSTR 2 negative ones, while no relation between treatment effectiveness and the expression of SSTR 5 was observed [39]. These results are in concordance with other case reports and smaller series of insulinoma patients reported in the literature [40-44]. In glucagonoma patients somatostatin analogue treatment is indicated to reduce the symptoms related to the characteristic skin rash (necrolytic migratory erythema) or diarrhoea [45-49]. In somatostatinomas symptoms are due to somatostatin hypersecretion (hyperglycaemia, cholelithiasis, diarrhoea and steatorrhoea, hypochlorhydria) or to the mass effect [50]. Although it seems a paradox to treat patients with symptoms related to elevated SST levels with a somatostatinoma, in 1998 Angeletti et al. showed that octreotide treatment was
effective in reducing somatostatin plasma levels and improving the related symptoms in three patients with metastatic somatostatinomas [51]. Furthermore, have been described nine cases of VIPoma in which octreotide was very successful as adjuvant therapy for symptoms control and for reducing the serum elevated VIP levels improving the diarrhea and the electrolyte imbalance [52-54].

The anti tumour effects of SST analogues

The antineoplastic activity of somatostatin analogues has been demonstrated in several experimental models in vivo and in vitro [55-60] but it is still little known regarding the antiproliferative role of SSA in GEP NETs, although increasing data suggest that such analogues can be tumouristatic, at least in some circumstances [61]. The antineoplastic action of SST analogues depends on the kind of tumour and the receptor subtypes they are bound to and occurs through direct and indirect mechanisms. While direct activities are mediated by specific membrane receptors and include antimytotic and apoptotic effects, indirect effects do not depend on the receptor binding but depend on the growth factor inhibition, antiangiogenic and immuno-modulating activities. SST analogues are able to inhibit the growth of Swann chondrosarcoma, used as experimental model of SSTR free tumour [62]. The mitosis inhibition is mediated by SSTRs 2 and 5 and results in the cell cycle arrest [55]. The loss of the SSTR 2 expression in some human adenocarcinomas seems to be responsible for loosing the regulation of cell proliferation [10-63]. The loss of SSTR 2 may consequently promote tumour growth and make it clear the therapeutic inefficacy of SST analogues in such kind of neoplasia. Apoptosis seems to be induced by two different processes: interaction with the SSTR 3 [56] and inhibition of the Insulin-like Growth Factor I (IGF I), known as a potent antiapoptotic hormone [64]. The pro-apoptotic activity of SST analogues seems to have clinical relevance, as shown by the interesting findings published by Eriksson et al. that reported an increase in apoptosis in bioptic samples of tissues by patients with GEP NETs after the treatment with SST analogues at high doses. It
followed that apoptosis is related to the biochemical response and the disease stabilization (70% of cases) [65, 66]. However, Faiss et al. observed an overall response rate (ORR) of 6.7%, comparable to that recorded at conventional doses [67], in 24 patients with GEP-NETs treated with high doses of lanreotide (15 mg/day). The indirect antiproliferative efficacy of SST analogues is shown by an antiangiogenic mechanism. Angiogenesis is essential for tumour growth and metastasis spread so, the growth can be actually controlled by reducing the vascularisation of the neoplastic tissue. In experimental models, octreotide shows a strong antiangiogenic effect, which is probably mediated by the inhibition of the Vascular Endothelial Growth Factor (VEGF) [68-70]. The treatment with octreotide would result in a significant reduction in VEGF levels compared to the baseline, since it is related to the survival of the patients [70]. It was observed that endothelial cells do not express the SSTR 2 that is present on the contrary, when they proliferate in order to form blood vessels. This could represent further opportunity to treat patients with octreotide that is able to recognize and inhibit new vessel formation both alone and with other drugs, thanks to its high affinity with such receptor (Table 3). Immunomodulation is another indirect mechanism of action of SST analogues. Preliminary evidence suggests that they stimulate the production of immune system components with antitumour effect, such as natural killer cells [71, 72], even if up to now it is not clear whether this can be clinically significant thus helping the antitumour efficacy of SST analogues. Few data exists on the functions mediated by the SSTR 4. However, no unanimity exists about the SST analogue ability to control (i.e. to slow) the tumour progression. In vitro studies reported that the response of different cell lines to the octreotide exposition produces a biphasic dose-response curve [73, 74]. Consequently, overdose or underdose of SST analogues may result in a suboptimal antineoplastic activity. Nevertheless, the negative results of some clinical studies in terms of tumour response could be due to the administration of too low doses to achieve receptor optimal saturation. After all, in other studies that used octreotide doses higher than 8 mg/day and lanreotide doses higher than 10 mg/day [75], no improvement of the SST analogue antitumour effect was observed. No study on the tumour response monitored plasma levels of an SST analogue up to now, in order to assess
that optimal drug therapeutic levels are reached but not exceeded [76]. Tumour shrinkage was demonstrated in less than 10% of the patients. However, a stabilisation of tumour growth occurs in up to 50% of the patients with neuroendocrine tumours of various locations. Stable disease was observed in 37–45% of the patients with documented tumour progression before SSA therapy (Table 4). The median duration of stabilisation was 26.5 months [29, 77-80]. In a study on a select group of patients with progressive disease, in the 47% of cases was demonstrated a stable disease when treated with a high dose of lanreotide (3-5 g/day) [81]. This result has been confirmed in patients with advanced mid gut carcinoids, who had a stabilisation of the disease for 6–24 months in the 75% of cases [82]. One patient with a pancreatic primary tumour, and distant extrahepatic metastases, showed a poor response to treatment in multivariate analysis. Age, size of the primary tumour, and Ki67 did not influence the response rate to SSA therapy [80]. A stabilisation of the disease was maintain throughout long-term follow-up in patients who achieve it after 6 months of treatment; these patients live longer than those unresponsive to therapy [80, 83]. Very recently Rinke et al performed for the first time a placebo-controlled, double-blind, phase III B study in 85 patients with well differentiated metastatic mid gut NETs using octreotide LAR 30 mg intramuscularly in monthly intervals (PROMID study). Median time to tumour progression in the octreotide LAR and placebo groups was 14.3 and 6 months, respectively. After 6 months of treatment, stable disease was observed in 66.7% of patients in the octreotide LAR group and 37.2% of patients in the placebo group. Functionally active and inactive tumours responded similarly. The most favorable effect was observed in patients with low hepatic tumour load and resected primary tumour. Octreotide LAR significantly lengthened time to tumour progression compared with placebo in patients with functionally active and inactive metastatic mid gut NETs [84]. Mid gut carcinoids express SSTRs in 80 to 100% of cases and SSTR 2 is the most frequently expressed [37]. The antiproliferative effect of somatostatin analogues on the growth of the mid gut carcinoids is unknown. A partial or complete responses were observed in less than 10% of the patients, while stabilisation of tumour growth was noticed in 24–57% of the patients [6]. Few data are available regarding the role of somatostatin analogues in the
treatment of gastrinomas. In a study of 15 malignant gastrinoma, in about 50% of these patients, octreotide had an antiproliferative effect, including one patient with tumour regression and seven patients with tumour stabilization [mean period 25 months] patients [85]. The long-acting somatostatin analogue octreotide-LAR was administered in a patient with multiple type A gastric carcinoids for a period of 9 months with a normalization of serum gastrin levels and permanent disappearance of the tumour [86]. Fykse et al. treated five patients with hypergastrinaemia and gastric carcinoids for a period of 1 year with monthly injections of octreotide-LAR with a significant reduction in tumour load, ECL cell density and normalization of circulating chromogranin A levels, indicating a possible direct antiproliferative effect of the treatment [87]. These results suggest that the somatostatin analogues could have an important antiproliferative effect. However, data on the effect of somatostatin analogues on tumour growth in patients with gastric carcinoids type C or poorly differentiated endocrine carcinomas are scanty. In poorly differentiated gastric carcinomas, treatment with somatostatin analogs is not considered. As surgical excision is the definitive treatment of insulinoma, there are few contrasting data in the literature regarding the inhibitory effect of the somatostatin analogues on the growth of these tumours. Grozinsky-Glasberg et al have conducted a study regarding the effects of somatostatin analogues on cell proliferation in the rat-derived insulinoma cell line (INS1). Their preliminary data show that octreotide has a significant inhibitory effect on cell proliferation, as assessed by cell counting and MTS assay, and on phosphorylation states of a number of proteins in the PI3K/Akt/mTOR pathway [88, 89]. In his work, Vezzosi founded that despite achieving hypoglycaemic control, insulinoma size remained unchanged or increased moderately despite normal blood glucose levels, concluding that somatostatin analogues, as medical treatment is not sufficient to prevent tumour growth in patients with malignant insulinomas [39]. In 2006, Romeo et al reported a complete clinical remission with regression of the metastatic lesions in the liver after one year in a patient affected by metastatic insulinoma with severe hypoglycaemia treated with octreotide LAR [89]. A more controversial area concerns the treatment of patients with non-functioning endocrine tumours of the pancreas as few studies have been
published in these patients. The prospective German Sandostatin multicentre phase II trial investigated the effects of octreotide for one year on tumour growth in 103 patients and included 15 patients with diagnosed non-functional pancreatic tumours [78]. Only 3 out of these 15 patients had a stable disease, in 8 patients a tumour progression occurred while the outcome of the remaining four patients was not clear. As previously reported, the SST analogue efficacy depends on the tumour receptor expression patterns, but these are rarely assessed, even if there is evidence of better results on survival obtained with selective treatments. An antiproliferative effect was achieved on hepatic metastatic cells in a patient with a carcinoid tumour, selected for the treatment with SST analogues after the immunohistochemical identification of the SSTRs 1, 2 and 5 subtypes expression on the neoplastic cell surface [90]. A complete clinical remission with regression of the metastatic lesions in the liver after one year of treatment was observed in a patient affected by metastatic insulinoma with severe hypoglycaemia treated with octreotide LAR expressing at immunohistochemical analysis of tissue specimens a strong membrane immunoreactivity for SSTR 2 in both the primary nodule and the metastases [89]. However, another study showed neither an antineoplastic effect nor an increase in survival percentage of treated patients [91]. It has been reported that in glucagonoma patients there are no data available on their SSTR expression patterns [48]. In 2006 we demonstrated, for the first time, a scattered immunopositivity for somatostatin receptors in a case of malignant glucagonoma. We had access to polyclonal antibodies specifically targeted against SSTR5 and SSTR2 and we were therefore able to localise these two receptors in our histological sections. The immunopositivity was detected for both receptor subtypes in the membrane and in the cytoplasm of glucagonoma cells. We then treated our patient with a combination therapy consisting of the somatostatin analogue octreotide and interferon-α. The patient had a complete resolution of skin rash, normalization of plasma glucagon, chromogranin A and neuron specific enolase levels and a metastatic disease stabilization. The patient’s quality of life significantly improved, and she was alive 40 months after debulking surgery [49].
The effects of higher than usual dose of SST analogues

It was suggested that higher than usual dose of somatostatin analogues treatments (>3,000 μg/day) may promote the anti-proliferative effect, especially in those patients responding to standard doses [2, 17, 18, 82, 92, 93]. An high-dose treatment with lanreotide (up to 12 mg/day) produced tumour size reduction in 5% and stabilization in 70% of the 19 patients. In responding patients was observed an induction of apoptosis in the tumours, a phenomenon not seen with regular doses of somatostatin analogs, but often produced by chemotherapeutic agents [66]. Subcutaneously injections of 5 mg lanreotide three times a day for a period of 1 year produced one complete and one partial remission in 30 patients with functional midgut NETs; stable disease in 11 patients (36%) and progression of the disease after 3–12 months of treatment in 11 patients [67]. The treatment with high-dose somatostatin analogues induced apoptosis in neuroendocrine tumours, while this was not found during treatment with low-dose somatostatin, in a study where biopsy specimens were taken before and during somatostatin analogue treatment [65]. In a highly select group of patients with progressive disease, 47% of the patients demonstrated at least stable disease when treated with a high dose of lanreotide (3-5 g/day) [81]. High-dose formula of octreotide has been recently reported to stabilize hormone production and tumour growth in 75% of patients with advanced midgut carcinoid tumours and progressive disease with stabilization for 6-24 months. [82]. These effects may be attributable to SSTR 2 which is the most frequently expressed subtype and/or SSTR 5, 1 and 3 which are also expressed [94, 95]. Data from a study with ultra-high dose octreotide pamoate (Onco-LAR; Novartis) at 160 mg intramuscularly every 2 weeks for 2 months followed by the same dose once monthly, appear to show some promise. Tumour size stabilization was obtained in 12 patients, a biochemical responses in 9 patients and/or stability in 11. No significant tumour reduction was noted. At 6 months, the median plasma concentrations of octreotide were 25–100 times higher than those obtained by using octreotide LAR at regular doses. A significant inhibition of angiogenesis was also showed through the down-regulation of proliferative factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor.
The highest response rates were reported using octreotide in doses greater than 30 mg/day or lanreotide in doses greater than 5 mg/day (and up to 15 mg/day) [63]. Tomassetti et al. have reported that after one-year therapy, the tumour completely disappeared in three patients suffering from gastric carcinoid, two of whom were treated with lanreotide 30 mg i.m. every 10 days [96]. In a recent paper it was reported that in patients with Hashimoto’s thyroiditis presenting entero-chromaffin-like cells (ECL) hyperplasia, considered a pre-neoplastic mark, the treatment with somatostatin analogue for 12 months resulted into the disappearance of ECL lesions (Hashimoto’s thyroiditis and entero-chromaffin-like cells hyperplasia: early detection and somatostatin analogue treatment [97]. Cirillo in his retrospective study on 165 patients with digestive NETs confirmed that somatostatin analogs can have a role in the treatment of digestive neuroendocrine tumors with low grades of malignancy, a low cellular proliferation index and a high specific receptorial density in vivo, showing a SD ranging from 60 to 66%. Moreover, an increase of the dosage of somatostatin analogs seems to have a better control both of the disease progression and the chronic refractory diarrhea [27]. In a very complete and well design paper of Ferolla et al, patients with well-differentiated neuroendocrine tumors, were treated with long-acting octreotide (LAR), conventionally administered at a dose of 30 mg every 28 days; the end point of this study was to evaluate a different schedule of octreotide LAR administration consistent with a shorter interval between administrations (21 days) in patients with a progressive disease at standard-dose interval. For this reason 28 patients who had tumor progression during therapy with LAR 30 mg every 28 days were enrolled. Clinical, biological and objective tumor response was evaluated after LAR 30 mg every 21 days. Time to progression was also evaluated after LAR 30 mg every 21 days and compared to LAR 30 mg every 28 days. The treatment with LAR 30 mg every 21 days resulted in complete and partial control of clinical symptoms in 40% and 60% of cases, respectively. Circulating neuroendocrine markers were significantly decreased in 30% of cases. A stabilization of disease was obtained in 93% and objective response in 7%. The median time to progression was significantly longer by using the shortened interval of LAR administration as compared to the standard one (30 vs 9 months, p<0.0001) and the treatment was
safe and well tolerated. The authors conclude that the shortened schedule of LAR administration was able to re-institute control of clinical symptoms, to decrease level of circulating neuroendocrine markers and to increase time to progression in patients previously escaping from a standard schedule treatment [98].

**Somatostatin analogs and diagnostic/therapeutic nuclear medicine**

SSTRs are able to form a receptor–ligand complex permitting the internalisation and the accumulation of the radiopharmaceutical peptide inside the tumour using this procedures for diagnosis and radiometabolic treatments of these tumors (fig. 2). Peptide-receptor radionuclide therapy (PRRT) is an important treatment strategy for tumours that express adequate densities of SSTRs and has proven to be safe and effective. It was initially performed using indium-111 [99, 100]. Recently, the development of somatostatin peptides with higher receptor affinity conjugated with radio-metal labelling chelators, such as DOTA, which may be allow stable labelling with gallium, yttrium or lutetium, changing the affinity profile for particular subtypes of SSTRs can permit new therapeutic options [101]. Waldherr et al evaluated the tumour response to targeted irradiation with the radiolabelled somatostatin analogue $^{90}$Y-DOTATOC in 41 patients with GEP NET and bronchial tumours. They reported an overall response rate of 24%. For endocrine pancreatic tumours it was 36 %. A complete remission was found in 2%, a partial remission (PR) in 22%, a minor response in 12%, stable disease in 49% and progressive disease in 15% of patients. The treatment was well tolerated and there was a significant reduction of symptoms and the 2-year survival time was $76 \pm 16\%$ [102]. 177Lu DOTATATE [177Lu]DOTA-Tyr(3)-octreotate, a selective analogue of SSTRs 2, in spite of its favourable affinity profile, at its maximum tolerated dose, it is limited by toxic effects on the kidney and bone marrow. Nevertheless, the results seem encouraging compared with historical therapeutic data [107]. Kwekkeboom et al obtained promising results using 177Lu DOTATATE [177Lu]DOTA-Tyr(3)-octreotate in 131 patients with NETs. A complete remission was observed in 2% of patients, a partial remission in 26%, a minor response in 19%, stable disease in 35%, and progressive disease in 18% of patients. Higher remission rates were positively
correlated with high uptake on pre-therapy SSTRs imaging, whereas progressive disease was significantly more frequent in patients with extensive disease. Median time to progression was more than 36 months [99]. The combination of \(^{90}\)Y- and \(^{177}\)Lu-labeled analogues [108] seems to have had superior antitumour effects when compared with either \(^{90}\)Y- or \(^{177}\)Lu-analogue in animals presenting with tumours of various sizes. It has been reported that \(^{177}\) Lutetium may be more effective for smaller tumours whereas \(^{90}\) Yttrium may be more effective for larger tumours [103, 104].

**Somatostatin analogues and interferon**

The combination of SSAs and interferon (IFN) has been used in an effort to enhance the antiproliferative effect of interferon therapy, to add the positive effect of SSAs on hypersecretory syndromes, and to reduce the dose of IFN and thus the number of IFN-related side-effects. Whether somatostatin analogues and IFN show a synergistic effect on tumour growth and in carcinoid syndrome symptom management is matter of debate. The combination therapy with somatostatin analogues and IFN is in fact limited by the small number of trials, with variable results. This combination seems of benefit in patients where the usual octreotide treatment failed to achieve a biochemical and symptomatic control [105].

**Conclusion**

Neuroendocrine tumors of the gastroenteropancreatic (GEP NETs) system comprise a rare group of malignant neoplasms. The somatostatin analogues have been shown to be very useful for symptomatic and biochemical improvement in patients with these tumours while preclinical and clinical studies provide conflicting results on their antitumour effects. The mechanisms of these effects are unknown, but probably are in part due to direct effects on proliferative signalling pathways, activation of apoptosis, and effects on angiogenesis. Biological response to
somatostatin analogs depends on distribution and level of expression of SSTRs subtypes in tumours, and the expression of selective somatostatin receptor-signaling pathway molecules. The high density of SSTR2 in endocrine tumours explains the use of SSTR2 specific analogues in the diagnosis and treatment of these tumours. However, the role of SSTR1,3 and 5 appears to be of increasing interest. The development of new peptidic and non-peptidic somatostatin analogues, subtype selective agonists, chimaeric analogues, or pan-somatostatin analogues will probably improve the diagnosis and treatment of GEP NETs, which express somatostatin receptors other than SSTR2. The combination of SSAs and IFN seems of benefit in patients where the treatment with somatostatin analogues alone failed to achieve a biochemical and symptomatic control while their synergistic effect on tumour growth is still unknown. The analysis of the SSTR status specifically for each patient, and studies of individual tumour biological behaviour, might be of therapeutic interest and could help to optimise treatment especially in unresectable tumours. Peptide-receptor–targeted radiotherapy for advanced disease using radiolabeled octapeptide analogues appears to be a significant progress in the treatment of GEP NETs but data are limited, mainly about the best time for its administration, or what is the most appropriate radioligand/combination to be used for each patient, and if and how the doses should be fractionated. Novel strategies based on SSTR2 receptor gene transfer to target tumor growth and angiogenesis might offer new perspectives of therapeutic interest mainly to treat unresectable tumours. Prospective studies including large number of patients regarding the optimal dosage and modes of administration of somatostatin analogues and the development of new slow release, SSTR subtype specific compounds are needed.

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**Table 1.** Somatostatin receptors in neuroendocrine gastroenteropancreatic tumours [%]

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</tr>
<tr>
<td>VIPoma</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>N-F</td>
<td>80</td>
<td>100</td>
<td>40</td>
<td>100</td>
<td>60</td>
</tr>
</tbody>
</table>

IP, vasoactive intestinal polypeptide. N-F, Non functioning. \(^a\)Using receptor subtype antibodies \(^b\)Malignant insulinoma

[Modified from Oberg K, Annals of Oncology, 2004]
**Tab. 2.** Somatostatin receptor subtypes mRNA in neuroendocrine tumours.

<table>
<thead>
<tr>
<th>Tumour</th>
<th>sst1</th>
<th>sst2</th>
<th>sst3</th>
<th>sst4</th>
<th>sst5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrinoma</td>
<td>79%</td>
<td>93%</td>
<td>36%</td>
<td>61%</td>
<td>93%</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>76%</td>
<td>81%</td>
<td>38%</td>
<td>58%</td>
<td>57%</td>
</tr>
<tr>
<td>Non-functioning pancreatic tumor</td>
<td>58%</td>
<td>88%</td>
<td>42%</td>
<td>48%</td>
<td>50%</td>
</tr>
<tr>
<td>Carcinoid tumor of the gut</td>
<td>76%</td>
<td>80%</td>
<td>43%</td>
<td>68%</td>
<td>77%</td>
</tr>
</tbody>
</table>

SST, somatostatin receptor. a Indicates the percentage of positive tumours for each SSTRs mRNA expression may overestimate the number of receptors present, depending on the technique used [PR-polymerase chain reaction, Northern blot, in-situ hybridization].

[Modified from Plockinger U. Biotherapy. Best Practice & Research Clinical Endocrinology & Metabolism 2007; Vol. 21, No. 1, pp. 145–162]
**Table 3.** Somatostatin receptor subtype-binding affinity of somatostatin analogues.

<table>
<thead>
<tr>
<th>Compound</th>
<th>SSTR1</th>
<th>SSTR2</th>
<th>SSTR3</th>
<th>SSTR4</th>
<th>SSTR5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin-14</td>
<td>2.26</td>
<td>0.23</td>
<td>1.43</td>
<td>1.77</td>
<td>0.88</td>
</tr>
<tr>
<td>Somatostatin-28</td>
<td>1.85</td>
<td>0.31</td>
<td>1.3</td>
<td>ND</td>
<td>0.4</td>
</tr>
<tr>
<td>Octreotide</td>
<td>1140</td>
<td>0.56</td>
<td>34</td>
<td>7030</td>
<td>7</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>2330</td>
<td>0.75</td>
<td>107</td>
<td>2100</td>
<td>5.2</td>
</tr>
<tr>
<td>Pasireotide</td>
<td>9.3</td>
<td>1</td>
<td>1.5</td>
<td>&gt;100</td>
<td>0.16</td>
</tr>
</tbody>
</table>

ND, not determined. [Modified from Grozinsky-Glasberg S., Endocrine-Related Cancer 2008 Sep;15[3]:701-20].
Table 4. Antiproliferative effect of somatostatin analogues in patients with progressive disease.

<table>
<thead>
<tr>
<th>SSA</th>
<th>Dosage</th>
<th>n</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanreotide</td>
<td>3000 µg/day</td>
<td>22</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>14</td>
<td>(97)</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>30 mg/2 weeks</td>
<td>35</td>
<td>0</td>
<td>1</td>
<td>20</td>
<td>14</td>
<td>(90)</td>
</tr>
<tr>
<td>Octreotide</td>
<td>600/1500 µg/day</td>
<td>52</td>
<td>0</td>
<td>0</td>
<td>19</td>
<td>33</td>
<td>(74)</td>
</tr>
<tr>
<td>Octreotide</td>
<td>1500/3000 µg/day</td>
<td>58</td>
<td>0</td>
<td>2</td>
<td>27</td>
<td>29</td>
<td>(26)</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>15000 µg/day</td>
<td>24</td>
<td>1</td>
<td>1</td>
<td>11</td>
<td>11</td>
<td>(97)</td>
</tr>
<tr>
<td>Octreotide</td>
<td>600 µg/day</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td>(73)</td>
</tr>
<tr>
<td>Octreotide</td>
<td>median dose of 250 µg/day three times daily</td>
<td>34</td>
<td>0</td>
<td>1</td>
<td>17</td>
<td>0</td>
<td>(75)</td>
</tr>
<tr>
<td>Octreotide LAR 30/ Lanreotide SR</td>
<td>60 mg /28 days</td>
<td>31</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>4</td>
<td>(76)</td>
</tr>
</tbody>
</table>

Total          | 256 | 1  | 6  | 115 | 105 |

Percentage [%] | 0.3 | 2  | 45 | 41  |

CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.
Figure 1.

Figure 2.

PET Gallium 68 DOTATOC showing the presence of multiple liver metastasis from neuroendocrine ileal tumor.