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Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours

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SUMMARY

Background
The discovery of somatostatin (SST) and the synthesis of a variety of analogues constituted a major therapeutic advance in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours (GEP-NETs). They currently provide the most efficient treatment to achieve symptomatic relief and have recently been demonstrated to inhibit tumour growth.

Aim
To review 35 years of experience regarding the clinical application and efficacy of SST analogues.

Methods
The PubMed database (1972–2009) was searched using somatostatin as a search term with combinations of terms including 'treatment'; 'neuroendocrine'; 'carcinoid'; 'tumor'; 'octreotide'; 'lanreotide' and 'pasireotide'.

Results
In a review of 15 studies including 481 patients, the slow-release formulations Sandostatin LAR and Somatuline SR/Autogel achieved symptomatic relief in 74.2% (61.9–92.8%) and 67.5% (40.0–100%), biochemical response in 51.4% (31.5–100%) and 39.0% (17.9–58%), and tumour response in 69.8% (47.0–87.5%) and 64.4% (48.0–87.0%) respectively. Novel SST analogues like SOM230 (pasireotide) that exhibit pan SST receptor activity and analogues with high affinity to specific somatostatin receptor (sstr) subtypes may further advance the field, but efficacy studies are lacking.

Conclusion
As more precise understanding of NET cell biology evolves and molecular biological tools advance, more accurate identification of individual tumours sstr profile will probably facilitate a more precise delineation of SST analogue treatment.

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OVERVIEW OF NEUROENDOCRINE TUMOUR THERAPY

In the century that has elapsed since the initial description of gastroenteropancreatic neuroendocrine tumours (GEP-NETs) (previously referred to under the generic terminology of carcinoid tumours), treatment has evolved from initial despair through polypharmacotherapy to the usage of targeted pharmacotherapeutic probes.[1, 2] These include SST analogues, growth factor inhibitors, antiangiogenic agents, interferons (IFNs) and a variety of kinase inhibitors.[3] However, despite diverse therapeutic strategies including chemotherapeutics, biotherapeutics, interventional radiology and a variety of surgical strategies, the overall clinical results leave opportunity for improvement.[4]

Although wide surgical resection is the optimal curative therapy for GEP-NETs, few lesions are detected early enough to avoid residual disease or hepatic metastasis. The early detection by endoscopy of small solitary non-invasive lesions in the stomach, duodenum and rectum has facilitated successful endoscopic local resection.[5, 6] In most individuals with pancreatic or small bowel NE neoplasia, the presence of metastatic disease at diagnosis makes complete resection unfeasible. Surgical resection of the primary and debulking of local and hepatic tumour load is therefore usually only undertaken as a palliative procedure to facilitate symptom control and prevent local adverse events caused by bleeding, perforation or bowel obstruction.[7] Despite multiple permutations and combinations of different regimens of single-agent or multi-agent chemotherapy, negligible or short-lasting effects on GEP-NETs are evident and even these are usually achieved at the expense of substantial diminution in quality of life because of drug toxicity.[3] The adverse events associated with these regimes usually exceed the efficacy of the agents.[8] The response rates for single agent therapy e.g. doxorubicin, 5-fluorouracil, dacarbazin, cisplatin, etoposide, streptozotocin and carboplatin are about 5–10%.[3] Although schedules with combination chemotherapy have slightly better (but only short-lasting) response rates (20–30%), the results are still disappointing.[3] No advantage in survival has ever been demonstrated in NET of midgut origin. In some instances, the IFN class of agents may have a role, but their usage is often associated with substantial adverse events. However, in some patients, IFN-alpha is of clinical value in combination with a somatostatin analogue (SSA) for the management of the carcinoid syndrome and in patients with sstr negative tumours for antiproliferative purposes. Both drugs are considered equally effective with respect to their antiproliferative efficacies.[9] The tolerability of pegylated IFN-alpha is better than that of the conventional regimen with s.c. injections, but is not approved in many countries.[10] Hepatic metastases are variably amenable to surgery, radio-frequency ablation or embolization either alone or in combination with chemotherapeutic agents or radioisotope loaded microspheres.[11]. Rarely, hepatic transplantation may be an option and considerable controversy exists as to its actual utility. Peptide receptor targeted radiotherapy (PRRT) for advanced disease using radiolabelled octapeptide analogues ($^{90}Y/^{177}Lu$-octreotide) is promising and useful in selected patients.[12] Rigorous data are, however, limited and studies to optimize the different regimens (isotope type, peptide receptor, number of cycles, doses, etc.) are still ongoing.[13] To date, novel growth factor antagonists and antiangiogenic agents have demonstrated limited efficacy with tumour remissions in <10% of the patients.[3] The recent evaluation of inhibitors of the mammalian target of rapamycin (mTOR), a serine/threonine protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription, such as everolimus (Afinitor®) alone or in combination with octreotide LAR appears in a phase II study an effective therapy with a 3 year survival rate of ~80% in patients with inoperable metastatic disease.[14]

Overall, were it not for the development of the SST analogue class of drugs that have been so effective in ameliorating symptoms and improving the quality of life, the therapy of NET disease would have advanced little. As a consequence, the keystone of current NET therapy therefore remains the long-acting SST analogues, which have been widely accepted to alleviate symptoms, stabilize tumour growth and substantially improve quality of life with minimal adverse effects. This overview details the evolution of SST analogues and their application to the management of NET disease documenting the accumulated clinical experience of the studies undertaken over 20 years and providing a global perspective on the utility and efficacy of this therapy. The PubMed database (1972–2009) was searched using somatostatin as search term combined with combinations of terms including 'treatment'; 'neuroendocrine'; 'carcinoid'; 'tumor'; 'octreotide'; 'lanreotide' and 'pasireotide'.

IDENTIFICATION OF NATURAL SST

Krulich in 1968 reported borderline statistically significant inhibition and stimulation of growth hormone (GH) release by crude extracts of different parts of the rat hypothalamus.[15] In 1972, at the Salk Institute in La Jolla, a GH-releasing antagonist (SST) was incidentally identified in sheep hypothalami during the search for a growth hormone releasing hormone (GHRH).[16, 17] Crude extracts of sheep hypothalamus added to *in vitro* anterior pituitary cells caused an inhibition of GH secretion. After purification, a single compound accounting for all the GH-release inhibiting activity of the crude extract was isolated, and its primary structure, a 14-amino acid peptide, was described.[17]

The 14 amino acids were bridged by a sulphur–sulphur bond and other mammalian SSTs were subsequently noted to have identical amino acid sequences and SST-like peptides from early vertebrates were also similar (Figure 1).[18, 19] Since spontaneous mutations are common over millions of years, the preservation of the peptide structure indicated that mutations must have been fatal. Similarly, the ubiquitous distribution in both the central nervous system and peripheral organs further suggested fundamental regulatory functions in vertebrate physiology[18] Localization studies demonstrated that SST was a product of specific hypothalamic neurones[20] and pancreatic D-cells[21] and diverse gut mucosal D-cells.[21] Subsequently, SST was detected in almost every tissue and organ system, nerve terminals and specialized glandular cells.[22, 23]

SST PHYSIOLOGY

The SST neuropeptide family (also known as somatotropin release-inhibiting factors) comprises peptides that originate from different posttranslational processing of a 116 amino acid precursor (pre-proSST) which is encoded by a single gene located in humans on chromosome 3q28. Pre-proSST is processed to proSST

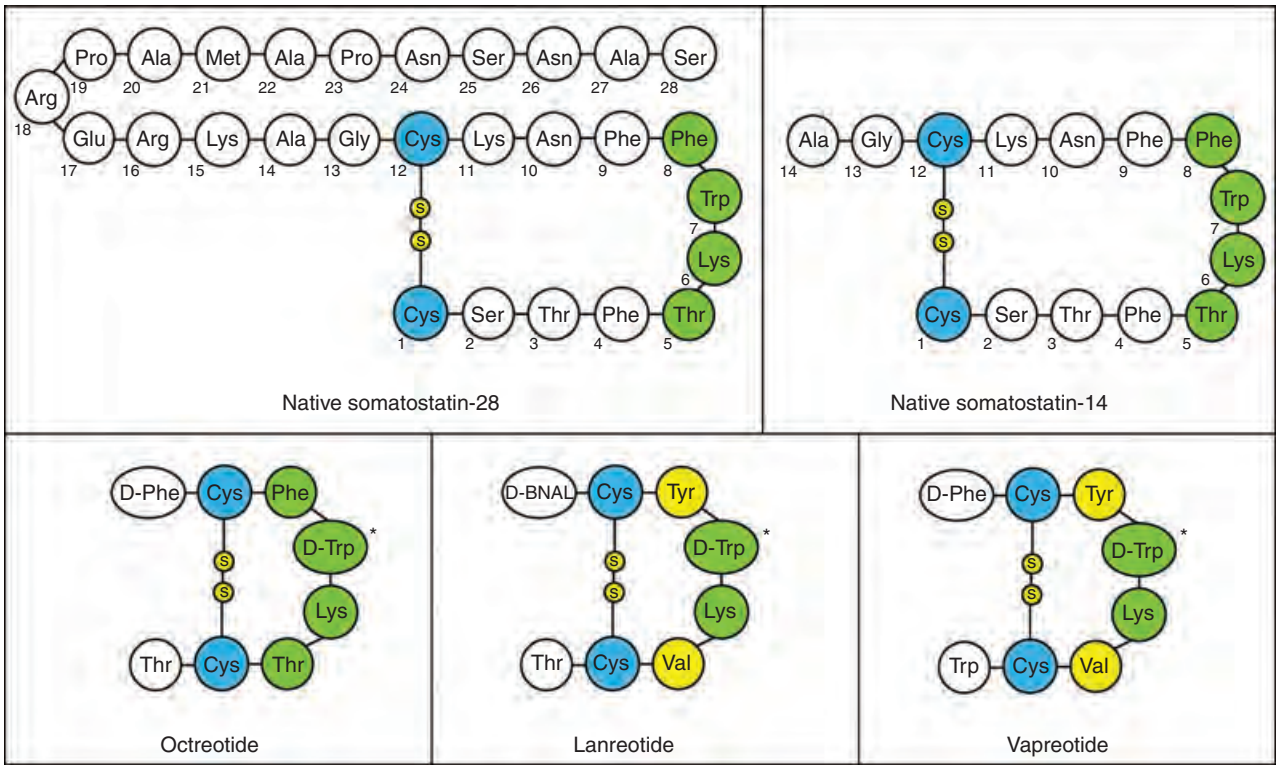

Figure 1. The structure of native somatostatin −28 and somatostatin −14, and the somatostatin analogues octreotide, lanreotide and vapreotide. The amino acid residues Phe, Trp, Lys and Thr, which comprise a β turn in the native molecule (green), are necessary for biological activity, with residues Trp and Lys are essential, while Phe and Thr can be substituted with Phe → Tyr and Thr → Val (yellow). The change from Trp to D-Trp in position 8 (*) is believed to prolong the action of the analogues compared to the native molecule.

(96 amino acids), which is further cleaved to produce two bioactive proteins, the predominant, but functionally less active SST molecule consisting of 14 amino acids (SST-14), and a larger more potent molecular form, SST-28.[24] The SSTs have a very short circulation half-life of 1.5–3 min rendering analysis of their physiological activity difficult.[25] The biological consequence is that SST-producing cells, or synaptic stores of SST, are generally close to the target cells, as exemplified by the D-cell, G-cell relationship of the gastric antral mucosa.[26] Although SST was initially identified as a physiological regulator of GH release from the anterior pituitary,[16] it subsequently became evident that it also inhibited islet beta and alpha cell insulin and glucagon secretion as well as pancreatic acinar cell amylase release.[23, 27] Finally, it became apparent that SST was a pan inhibitory agent for all known gastrointestinal tract hormones.[23]

The majority of circulating SST originates from the stomach and intestine, with plasma levels of 30–100 ρmol/mL which increase postprandially by ~100% up to 2 h.[28, 29] However, in general, SST effects are local and produced mainly at the specific site of secretion where it acts at nanomolar concentrations, prior to rapid inactivation by local endosomal endopeptidases (e.g. endothelin-converting enzyme-1),[30] thereby minimizing superfluous systemic effects. The action of SST is consequently brief and rapid and is followed by rebound hypersecretion, indicating that it inhibits release rather than synthesis.[31]

Twenty years after the discovery of SST in 1972, molecular cloning facilitated the identification of its receptor structure.[32] Subsequently, it has become apparent that in mammals, SST mediates its inhibitory effects through binding to at least five high-affinity G-protein-coupled membrane receptors (sstr1–5).[33] Each receptor consists of a single polypeptide chain with seven trans-membrane spanning domains with the extracellular domains exhibiting the ligand-binding sites and the intracellular sites providing linkage to second messenger activation. Although each of the sstrs is encoded by separate genes on different chromosomes,[34] sstr2 is unique as it can be spliced upon transcription with two resulting splice variants (2A and 2B). The sstrs share about 40–60% homology, but mediate different biological actions upon activation.[35] All five sstrs have been identified throughout the CNS, the GI tract and endocrine and exocrine glands, as well as on inflammatory and immune cells[36] and all bind the natural peptides, SST-14, SST-28 and cortistatin with similar high affinity (nM range). However, only sstr5 displays a 10-fold higher affinity for SST-28 suggesting a potentially different role for this peptide receptor.[22, 37] The physiological actions of SST are most probably both sstr subtype-specific and the result of the interaction between two or more sstrs within a given cell membrane following SST ligand binding.[38] It is also evident that G-protein-coupled receptors like sstrs are highly dependent upon the intracellular environment in which they are expressed, resulting in tissue-specific responses even if they emanate from the same receptor subtype.[39] The identification and elucidation of the intracellular signal transduction pathways following sstr activation have mainly been derived from *in vitro* studies. The diverse inhibitory effects of SST on neurotransmission, motor and cognitive functions, smooth muscle contractility, glandular and exocrine secretions, intestinal motility and absorption of nutrients and ions are all mainly mediated by cyclic adenosine monophosphate (cAMP) (a second messenger that is important in many biological processes and used for intracellular signal transduction) and Ca^{2+} reduction with activation of protein phosphatases (Figure 2a).[40, 41] At least four intracellular effector pathways have been described: (i) inhibition of Adenyl cyclase with a subsequent fall in intracellular cAMP resulting in downregulation of PKA (a cAMP-dependent protein kinase); (ii) activation of K^+ and Ca^{2+} channels leading to a fall in transmembrane Ca^{2+} influx resulting in a reduction of intracellular Ca^{2+}; (iii) activation of protein phosphatases (calcineurin which inhibit exocytosis and serine/threonine phosphatases which influence Ca^{2+} and K^+ channels); and (iv) activation of intracellular tyrosine phosphatase, which through different pathways inhibits proliferation (Figure 2b). In addition, sstrs may affect the activity of phospholipase C, cGMP and phospholipase A2 (enzymes important for signal transduction) in *in vitro* systems.[42] In summary, the current understanding of SST/sstr induced intracellular signalling is built on *in vitro* models and the *in vivo* relevance remains to be elucidated.

Of clinicopathological significance was the observation that most tumours originating from SST target tissues express a high density of SST receptors.[43] Thus, diverse neoplasia including NETs of the GEP axis and bronchopulmonary system, pituitary tumours, meningiomas, medulloblastomas, medullary thyroid carcinomas, adenocarcinomas of the breast, ovary and colon expressed high levels of sstrs.[43] On the contrary,

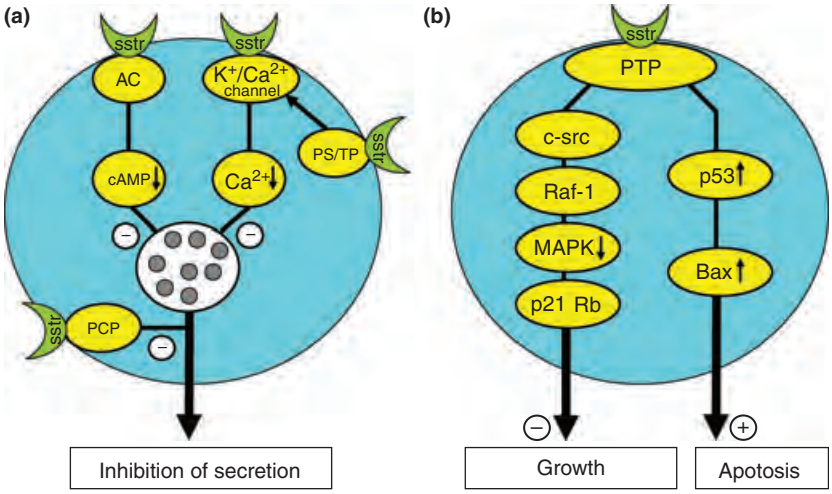

Figure 2. (a) proposed intracellular effector pathways involved in SST induced inhibition of secretion; inhibition of Adenyl cyclase (AC) with a subsequent fall in intracellular cAMP; activation of K and Ca channels leading to a fall in transmembrane Ca^{2+} influx resulting in a reduction of intracellular Ca^{2+}; activation of protein phosphatases [calcineurin (PCP), which inhibits exocytosis and serine/threonine phosphatases (PS/TP), which influence Ca^{2+} and K^{+} channels]. (b) Activation of intracellular protein tyrosine phosphatase (PTP), which through different pathways inhibits growth and induces apoptosis.

poorly differentiated or undifferentiated tumours express SST receptors less often and at a lower density than well-differentiated (less malignant) neoplasia.

Although experimental investigation has demonstrated that SST exerts cytostatic effects on tumour cells, however, its role in growth arrest is poorly defined and incompletely understood.[44, 45] Overall, a variety of different anti-proliferative mechanisms exist depending on sst receptor subtype and cell type. These involve hyperphosphorylation of the retinoblastoma gene product and G_1 cell cycle arrest, but may also be a consequence of sstr3 (and to a lesser extent sstr2)-mediated apoptosis.[24, 44] Depending on the particular splice variant of the sstr2 receptor that is activated, the effect on proliferation may actually be stimulation instead of the usually seen inhibition.[46] In addition, SST may exert an indirect antiproliferative effect by inhibiting the release of growth factors and various trophic hormones [GH, insulin-like growth factor-1 (IGF-1), insulin, gastrin, epidermal growth factor] both from the neoplastic cell and from the surrounding tumour matrix.[47]

In this respect, the impact of SST on tumour related angiogenesis is of considerable relevance given the critical role of this biological phenomenon in neoplastic progression. *In vitro* experiments indicate that SST may display anti-angiogenic properties by inhibiting the production and release of pro-angiogenic factors as well as expression of the relevant receptors. Thus, in immortalized HMEC (human dermal microvascular endothelial cells), vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor-2 (VEGFR-2) expression and VEGF release are inhibited by sstr1 agonists.[48] Octreotide reduced the proliferation of HUVEC (human umbilical vein endothelial cells) and in different animal models of experimental angiogenesis octreotide was able to reduce the extent of neovascularization.[49] Recently, it has been demonstrated in an animal model of portal hypertension that octreotide reduces markedly splanchnic neovascularization and VEGF expression, and the efficacy was linked to the presence of sstr2.[50] Similarly, in the pancreatic cancer cell line PC-3, sstr2 expression correlates with VEGF and matrix metalloproteinase-2 expression.[51]

DEVELOPMENTAL HISTORY OF THE SST ANALOGUES

Given the widespread inhibitory activity of SST, consideration of its utility as a pharmacotherapeutic agent had not escaped attention. However, the clinical utility of native SST was clearly limited given its extremely rapid blood clearance and post infusion hormonal hypersecretion rebound.[52] The development of stable and potent analogues therefore became nec-

essary for therapeutic efficacy. In 1974, Sandoz initiated a project to synthesize longer-acting synthetic analogues with higher potency than native SST.[53] Five years later, a short octapeptide analogue with full SST-like biological activity was reported by Vale *et al.*[54] Structure–activity studies of SST-14 demonstrated that the amino acid residues Phe, Trp, Lys and Thr, which comprise a β turn, were necessary for biological activity. Residues Trp and Lys are essential, while Phe and Thr could be substituted with, e.g. Tyr and Ser or Val respectively (Figure 1). Of the hundreds of peptides synthesized, SMS 201–995 (octreotide) was a molecule that exhibited a three-fold potency in the inhibition of glucose-stimulated insulin secretion and a 19-fold potency in GH secretion inhibition compared to native SST.[55] Octreotide was initially prepared as an acetate salt solution for administration by deep subcutaneous (intra-fat) or intravenous injections.

The introduction of two 'unnatural' amino acids (D-Phe at the N-terminal and L-Thr at the C-terminal end) and the substitution of L-tryptophan by D-tryptophan in position 8 rendered the peptide resistant to degradation.[56] Thus, by the early 1980s, a number of 'short' synthetic analogues of SST including octreotide, vapreotide, lanreotide, seglitide, BIM23268 and NC8-12 were developed (Table 1).[22]

All these cyclic octapeptides were more resistant to peptidases and their half-lives and hence biological activity substantially longer than the native tetradecapeptide SST (1.5–2 h vs. 1–2 min), thus enhancing pharmacological efficacy.[55]

Continuous infusion of SST analogues proved more efficient than repeated s.c. injections, which suggested that preparations providing a sustained level of SST analogue would be more advantageous than intermittent pulses of drug.[57] This observation prompted the subsequent development of long-acting depot formulations [octreotide LAR, lanreotide microparticles (MP) and lanreotide autogel] of SST analogues which further improved the clinical utility and led to a substantial improvement in quality of life with relatively mild adverse effects.[58–60] The structure of octreotide LAR is octreotide incorporated into microspheres of the biodegradable polymer Poly DL-lactide-co-glycolide, a process that had previously been used successfully to prepare a long-acting preparation of bromocriptine.[61] The addition of these microspheres to a diluent (carboxymethylcellulose sodium, mannitol and water) forms a suspension that can be administered as an intramuscular injection of octreotide LAR. Once injected, the microspheres biodegrade mostly through hydrolysis.

After an i.m. injection of octreotide LAR, a short-lasting rise in octreotide levels is seen because of release from the microsphere surface; thereafter, levels slowly increase for up to 14 days and remain constantly elevated for 28–42 days. Lanreotide has been developed in two slow-release formulations, lanreotide MP and lanreotide autogel. Lanreotide MP requires reconstitution prior to usage and is injected i.m. every 14 days. Lanreotide autogel is a viscous aqueous solution composed of only lanreotide and water that is injected every 4 weeks and was designed to replace lanreotide MP. The combination of hydrophobic and hydrophilic residues, together with the disulfide bridge, leads to self-association of lanreotide molecules when mixed with water and the formation of a semi-solid gel which can be self administered via deep subcutaneous injection.

To provide an agent that might offer a broader sstr profile with a more universal binding profile similar to that of natural SST, structural elements of SST-14 were incorporated into a stable cyclohexapeptide template in the form of modified unnatural amino acids. Overall, the concept was to develop a small, metabolically stable SST analogue and culminated in the introduction of the novel cyclohexapeptide SOM230 (pasireotide) in 2004. Pasireotide binds with high affinity to sstr subtypes sstr1, sstr2, sstr3 and sstr5 and displays a 30- to 40-fold higher affinity for sstr1 and sstr5 than octreotide or lanreotide.[8] Pasireotide exhibits nanomolar potency for types 1, 2, 3 and 5 with no agonist activity at the type 4 receptor[40, 62] and it has been proposed that the high affinity for type 5 receptors may prove therapeutically advantageous.[8, 62, 63]

Peptide SST analogues exhibit numerous limitations in clinical use, including lack of oral bioavailability, relatively short half-life and immunogenicity. Tachyphylaxis is a clinical limitation that is particularly relevant to the SST analogue class of agents. The strategies to optimize efficacy therefore include optimization of the peptide structure and delivery mode as well as the development of nonpeptide analogues. The latter class of agents may be particularly advantageous as they can be synthesized to exhibit more specific sstr binding, have longer half-lives, be orally bioavailable and display less immunogenicity. Carbohydrates can be used for nonpeptide scaffolding as they contain

Table 1. The binding affinities and *in vitro* and clinical application of different somatostatin analogues and chimeric compounds

Compound	Peptide	Sstr1	Sstr2	Sstr3	Sstr4	Sstr5	D2DR	Administration	Clinical use
Sstr2,5 preferential agonists									
Octreotide (SMS 201–995)	Octapeptide	290–1140	0.4–2.1	4.4.–34.5	>1000	5.6–32		s.c.	Carcinoid syndrome Acromegaly
Lanreotide (BIM 23014)	Octapeptide	500–2129	0.5–1.8	43–107	66–2100	0.6–14		s.c.	Carcinoid syndrome Acromegaly
Vapreotide Octastatin (RC-160)	Octapeptide	481–>1000	5.4	31	45–351	0.7–7.5		i.v. s.c.	Oesophageal variceal bleeding (Carcinoid syndrome); *In vitro*: CFPAC-1 human pancreatic cancer
Seglitide (MK-678)	Hexapeptide	>1000	0.2–1.5	27–36	127–>1000	0.06–23			Pituitary cell line GH_3, AtT20 cells
BIM-23197	Synthetic Peptide	>1000	0.19	26.8	897	9.8		–	CHO-K1 cells, Pituitary cell cultures
BIM- 23244	Peptide	>1000	0.29	133	>1000	0.67			*In vitro*: Pituitary tumour cell culture
Other bi-selective sstr agonists									
NC8-12	Peptide	>1000	0.024	0.09	>1000	>1000			CHO-K1 cells *In vitro*: AtT20 cells
L-817,818	Non-peptide	3.3	52	64	82	0.4			CHO-K1 cells
Sstr pan inhibitors									
Pasireotide (SOM230); Pasireotide LAR	Cyclo-hexapeptide	9.3	1	15	100	0.16		s.c. IM	Carcinoid syndrome (clinical trials) Pituitary tumours (Clinical trials)
BIM-23A779	Peptide	2.5	0.3	0.6	20	0.6			*In vitro* (AtT-20 cells)
KE108	Peptide	2.6	0.9	1.5	1.6	0.65			*In vitro*:corticotrophs CHO-K1, CCL-39
KE119		6.9	1.1	2.5	3.8	2.6			CHO-K1, CCL-39
SSTR selective agonists									
CH275	Peptide	3.2–4.3	>1000	>1000	4.3–874	>1000			CHO-K1 cells
L-797,591	Non-peptide	1.4	1875	2240	170	3600			
BIM -23120	Peptide	>1000	0.34	412	>1000	213,5			CHO-K1 cells
L-779,976	Non-peptide	2760	0.05	729	310	4260			
BIM-23056	Peptide	110–>1000	132–>1000	10.8–177	17–234	5.7–158			*Agonist + Antagonist In vitro*:
L-796,778	Non-Peptide	1255	>10,000	24	8650	1200			CHO-K1 cells
NNC 26-9100	Non-peptide	5000	3300	6800	100	4100			*In vitro*: GH, Insulin secretion
L-803,087	Agonists	199	4720	1280	0.7	3880			CHO-K1 cells
BIM-23268	Peptide	18.4	15.1	61.6	16.3	0.37			Primary pit. cell cultures (GH secretion)

Table 1. (*Continued*)

Compound	Peptide	Sstr1	Sstr2	Sstr3	Sstr4	Sstr5	D2DR	Administration	Clinical use
BIM-23206	Peptide	>1000	166	>1000	>1000	2.4			
Chimeric molecules (dopastatins)									
BIM-23A760	Peptide	622	0.03	160	>1000	42	15		CHO-K1; Primary pituitary cell cultures; Phase I/II clinical trials (Acromegaly)
BIM-23A387	Peptide	293	0.2	77	>1000	26	22		Pituitary adenoma, lung carcinoma: *in vitro* studies
BIM-23A761	Peptide	462	0.06	52	>1000	3.7	27		Pituitary adenoma: *in vitro* study

Literature from references.[22, 120–132]
CT, carcinoid tumour; EPT, endocrine pancreatic tumour; ICC, islet cell carcinoma.

well-defined and readily convertible substituents with a rigid pyran ring.[64] A cross-talk between different G-protein-coupled receptor families may result in enhanced functional activity. It has been demonstrated that dopamine (DA) receptor D2R and sstr5 interact physically through hetero-oligomerization to create a novel receptor with enhanced functional activity.[65] Recently, a number of new subtype selective analogues and antagonists, as well as bi-specific and hybrid SST/DA compounds have been developed, and their efficacies are under investigation.[66] These ligands include sstr selective, bi-specific, universal as well as chimeric DA somatostatin ligands (Table 1). *In vitro* studies using pituitary human adenoma cells demonstrate a stronger inhibition of hormone secretion [prolactin, GH, adrenocorticotropic hormone (ACTH)] by SSAs targeting both sstr2 and 5, compared with sstr2 preferential SSA. D2R is expressed in the majority of low and intermediate grade NETs and is co-expressed with sstr2 and sstr5 in most cases.[67] Thus, dopastatins seem to be an attractive future treatment in NET disease.

THE EFFECT OF SST ANALOGUES ON BIOACTIVE PEPTIDE SECRETION

In early studies, octreotide inhibited the release of GH, glucagon and insulin in monkeys 45, 11 and 1.3 times more powerfully respectively, than SST-14.[55] Long-term therapy was demonstrated to control symptoms in ~65% of acromegalic patients.[68]

Pancreatic islet-cell tumours and gastrointestinal NETs retain many of the characteristics of the NE cells from which they originate, and >80% of these lesions express SST receptors.[69] Given this level of sstr expression, attention was directed to the effects of SST analogues in GEP-NETs.

In 1978, it was first reported that SST-14 was able to prevent spontaneous and provoked flushing in patients with carcinoid tumours.[70] It was further demonstrated that i.v. SST led to an improvement of secretory diarrhoea in patients with carcinoid syndrome.[71, 72] Shortly thereafter, it was demonstrated that the s.c. injection of the synthetic long-acting SSA SMS 201–995 (SMS) improved carcinoid flushing.[73] and diarrhoea in pancreatic endocrine tumours.[74] In addition, an acute carcinoid crisis with severe diarrhoea, dehydration and hypotension occurring with induction of anaesthesia was shown to be successfully treated with SMS.[75] Treatment with SMS proved to be remarkably effective

in producing clinical responses in larger patient cohorts. In a study of 25 patients with histologically proven metastatic carcinoid tumours and the carcinoid syndrome, the drug was administered at a dose of 150 μg three times daily. Flushing and diarrhoea were promptly relieved in 88% of the patients. A decrease of 50% or more in urinary 5-hydroxyindoleacetic acid (5-HIAA) levels was found in 72% for a median duration of more than 12 months (range: 1 to >18). No serious toxicity was reported.[76] In an analysis of several studies, treatment with SMS is reported in 59 evaluable patients of 62 with carcinoid tumours with symptom control in 92% of the patients using dosages of 50–500 μg s.c. two to three times daily for at least 1 month up to 18 months.[77] Biochemical response had been achieved in 66% of the patients. Reduction in tumour size was reported in 8%, stable disease in 85%.

Numerous other reports in patients with the carcinoid syndrome have demonstrated that SMS 201–995 effectively reduces diarrhoea and flushing (Table 2) and is useful in treating carcinoid crisis. The beneficial clinical effects are associated with a decrease in the release of secreted mediators.

Somatostatin analogues were early demonstrated to lower the levels of urinary 5-HIAA, the metabolite of serotonin.[76] Similarly, SSAs control hypoglycaemia in ~50% of patients with insulinoma.[78] The first line therapy for gastrinomas is proton pump inhibitors to control gastric acid secretion. SSA may, however, be useful to control both hormone secretion and tumour growth in metastatic disease.[79] SSAs may also improve glucagonoma induced diarrhoea and necrolytic migratory erythema[80] and paradoxically, octreotide has been shown to reduce SST secretion from somatostatinomas.[81] In NETs producing vasoactive intestinal peptide (VIP), VIPomas, SSAs significantly reduce (>90% control) the associated symptoms (Werner–Morrison syndrome) of severe watery diarrhoea, hypokalaemia, achlorhydria and metabolic acidosis.[82]

There is substantial variation in sstr subtype expression between different tumours and even between tumours of the same type.[83] The depiction of tumour sstr expression might enable more efficient treatment with tailored selected SST analogues.

TACHYPHYLAXIS AND SIDE EFFECTS

In a substantial number of NET patients, an escape from treatment within months may occur; this may be because of desensitization of the inhibition of the secretion of tumour-related hormones by SSTs, whereas other responding patients can be controlled for periods extending several years.[84] The potential mechanisms responsible for this desensitization as well as for the considerable variability in the duration of the responses are not known at present. This desensitization may be overcome by increase in the dosage of octreotide in some patients. Significant tumour progression over time in slowly progressive midgut tumours might contribute to the decrease in efficacy within months to years.

Most frequent observed adverse effects (>1/100) are abdominal pain with cramps, constipation, diarrhoea, steatorrhoea, nausea, injection site irritation and local pain, nausea and vomiting. Less frequent: hypothyroidism, cholecystitis and cholelithiasis.[85] Rare adverse effects (<1/1000): acute pancreatitis, alopecia, acute hepatitis, hyperbilirubinaemia, hyperglycaemia, hypoglycaemia, prolonged QT interval (the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle) and arrhythmias.[86–88]

DETAILS OF INDIVIDUAL AGENTS

Octreotide

Octreotide (SMS201–995) was finally synthesized in 1979, thus culminating a project that was initiated in 1975 by the chemist Wilfried Bauer.[55] Octreotide retained the Phe-Trp-Lys-Thr portion of the native molecule which constituted the essential pharmacophore[89] and exhibited high-affinity binding for sstr2 and sstr5, low affinity for sstr1 and sstr4 and medium affinity for sstr3.[40] Octreotide was the first available SST analogue and was introduced into clinical practice in 1983 for treatment of hormone-producing pituitary, pancreatic and intestinal neuroendocrine tumours.[55] As octreotide is incompletely absorbed after oral administration, its efficacy relied upon intravenous or subcutaneous injections. Nevertheless, the ability of patients to self inject subcutaneously was a great achievement as it enabled home usage.

Once absorbed, octreotide is distributed mainly in the plasma where 65% is protein bound. Approximately one-third is excreted unchanged in the urine and in patients with renal failure, clearance can be reduced by ~50%. The elimination half time after a

Table 2. Clinical studies on the efficacy of different somatostatin analogues and formulations

Study	*N*	SSA	Dose	Symptomatic response (%)	Biochemical response (%)				Tumour response (%)		
					SD	PR	CR	BR	SD	PR	CR
Kvols[76]	25	OCT	3 × 150 μg	88		72					
Vinik[133]	14	OCT	2 × 100 to 4 × 250 μg	100 (flush) 83 (diarrhoea)				75	50	20^	
Janson[114]	43	OCT	100–1200 μg	70 (flush) 69 (diarrhoea)				37			
Arnold[134]	103 (39 CS)	OCT	3 × 200–500 μg	85*	38.5	28.2	5.1	33.3†	36.5/23‡	0	0
Rubin[90]	24	OCT	~567 μg	58.3							
Eriksson[135]	10 EPT	OCT	2 × 50 μg/day	70				40	100		0
Kvols[136]	22 ICC	OCT	3 × 50–150 μg/day			64					
O'Toole[97]	25	OCT	2–3 × 200 μg/day	68 (flush) 50 (diarrhoea)				50			
Arnold[112]	20	OCT	3 × 200 μg/day	83 (flush) 57.1 (diarrhoea)		33.3			43.1/15.7	2	0
Öberg[137]	23	OCT	2 × 50–100 μg/day	50		28§					
Anthony[138]	13	OCT	3 × 500–2000 μg/day						15	31	0
Di Bartalomeo[106]	16 CT	OCT	3 × 500 to 3 × 1000 μg/day	73 50 (flush) 40 (diarrhoea)	23	46	31	77	47	3	0
Aparicio[108]	17	OCT	3 × 100 μg	–	–	–	–	–	59	0	0
Saltz[105]	34 (20 CT, 13 EPT, 1 CUP)	OCT	3 × 150–250 μg/day	71¶				33	50	0	0
Garland[139]	27 (13 with prior s.c. OCT)	OCT LAR	20–30 mg q 28 days	77 (prior s.c. OCT) 92.8 (OCT-naïve)	31	19	12.5	31			
Ricci[140]**	15 (7CT, 8 EPT)	OCT LAR	20 mg q 28 days	75	33	8	33	41	40	7	0
Rubin[90]	18	OCT LAR	10	66.7							
	15		20 mg q 28 days	71.4					–	–	–
	22		30	61.9							
Tomassetti[141]	16 (10 CT)	OCT LAR	20 mg q 28 days	87.5 (flush) 90 (diarrhoea)				100 (11/11)	87.5	0	
Welin[110]	12	OCT PAM	160 mg	83	58	33			75	0	0
Anthony[138]	13	LAN	3 × 750–3000 μg/day						8	31	0
Eriksson[111] l††	19 (13 CT+6 EPT)	LAN high dose	750 μg → 12 000 μg/day		–			58	70†	5†	0
Faiss[142]	30	LAN	3 × 5000 μg/day	63					37	3.3	3.3
Faiss[9]	25	LAN	3 × 1000 μg/day						28	4	0

Table 2. (*Continued*)

Study	*N*	SSA	Dose	Symptomatic response (%)	Biochemical response (%)				Tumour response (%)		
					SD	PR	CR	BR	SD	PR	CR
Scherübl[143]	12	LAN depot	30 mg q 7–14 days	85.7 (flush) 41.7 (diarrhoea)	–	–		–	58	0	0
Ruszniewski[144]	39	LAN SR	30 mg q 14 days	54 (flush) 56 (diarrhoea)	57 46	18 42		(1 mo) 42 (6 mo)		0	
Tomassetti[145]	18 (10 CT, 5 NF)	LAN SR‡‡	30 mg q 10 days	100				33§§	78	0	
Wymenga[146]	55 (48 CT)	LAN SR	30 mg q 14 days	53.8 47.6 (flush) 42.1 (diarrhoea)	52	27		47	81	6	
Ricci et al[60]¶¶	25 (12 CT, 13 EPT)	LAN	30 mg q 14 days	70	10.5	31.5	10.5	42	40	8	0
Ducreux[147]	39 (25 F, 14 NF)	LAN	30 mg q 14 days q 10 days	40 (only CR)	24	40		40	48.7***	5***	
Aparicio[108]	11	LAN	30 mg q 14 days	–	–	–	–	–	55	0	0
O'Toole[97]	26	LAN	30 mg q 10 days	53.8 (flush) 45.4 (diarrhoea)				58			
Ruszniewski[148]	71	LAN PR	60–120 mg q 28 days	38: 65/81††† (flush) 18/75††† (diarrhoea)				30	–		
Bajetta[59]	30	LAN MP	60 mg q 21 days		39.3	14.3	3.6	17.9	64.3	3.6	0
	30	LAN AG	120 mg q 42 days		18.5	29.6	11.1	40.7	67.9	0	0
Aparicio[108]	7	OCT LAN	3 × 100 μg + 30 mg q 14 days	–	–	–	–	–	71.4	0	0

Biochemical markers: PR = reduction >50%; BR = overall biochemical response (PR + CR); CR = complete response; CT = carcinoid tumor; EPT = endocrine pancreatic tumor; CS = carcinoid syndrome; LAN = lanreotide; PR = prolonged release; MP = microparticles; AG = Autogel; OCT = octreotide; LAR = long acting repeatable; F = functioning; NF = Non-functioning.

* Symptoms assessed only in 20 patients with diarrhoea and 27 with flush.

† Assessment at 12 months.

‡ Best response/response at 12 months.

§ Decrease of 5-HIAA and/or *tumour* size.

^any regression.

¶ Combined symptom or biochemical control.

** After failure of lanreotide SR.

†† Prior treatment with OCT in 9 patients, IFN in 15, chemotherapy in 5.

‡‡ Prior treatment with octreotide in 15 patients.

§§ Significant biochemical response only in non-carcinoid tumours.

¶¶ Prior treatment with OCT s.c. or chemotherapy or other in 13 patients.

*** Prior progressive disease documented.

††† Any improvement from baseline by end of the study.

subcutaneous injection is ~2 h and contrary to the native peptide, no rebound hypersecretion of hormone is evident.[35] Although octreotide is far more potent than the native molecule (~20 times)[55] and has been infused in doses >100 μg/h, the drug has proven very safe in clinical studies. The standard dose of octreotide varies from 0.1 to 0.3 mg subcutaneously two to three times daily, but doses up to 3 mg/day may be necessary for symptom control. The development of a depot formulation of octreotide, octreotide LAR (long acting repeatable) administered up to 30–60 mg every 4 weeks has, to a large extent, eliminated the need for daily injections. However, symptom breakthrough in the weeks before a steady state is achieved or in the last week of the cycle sometimes necessitates 'rescue' with an additional 50 or 100 μg (up to 1000 μg) dose of a short-acting analogue such as Sandostatin or by increasing the dose and/or frequency of the depot injection. A randomized study comparing daily injections with octreotide to octreotide LAR every 4 weeks in the symptomatic treatment of 93 patients noted at least as good symptomatic efficacy for depot octreotide at various dosages (10, 20, 30 mg) compared to s.c. octreotide.[90]

Lanreotide

A series of octapeptide analogues based on octreotide was synthesized by Coy and co-workers; the most active analogue of this series was Lanreotide (BIM 23014).[91] Similar to octreotide, lanreotide also displays high-affinity binding for type 2 and type 5 receptors, low affinity for types 1 and 4 and medium affinity for type 3.[40] Lanreotide is a long-acting SST analogue administered every 10–14 days that has a similar efficacy to octreotide in the treatment of NETs and acromegaly.[92] A new slow-release depot preparation of lanreotide, 'Lanreotide Autogel' administered subcutaneously at a dose of 60, 90 or 120 mg once a month was thereafter produced. Lanreotide Autogel is available in a small volume, prefilled syringe and is administered by deep s.c. injection. It has been demonstrated to be as efficacious and well tolerated as lanreotide in the treatment of acromegaly and gastrointestinal NETs.[59, 93, 94]

Pasireotide

The transposition of important functional groups from SST-14 into a reduced size, stable cyclohexapeptide template resulted in the development of a novel metabolically stable cyclohexapeptide SOM230 (pasireotide) with broad sstr binding and a unique inhibitory profile.[8] Pasireotide has high affinity to sstr1, sstr2, sstr3 and sstr5, and displays a 30- to 40-fold higher affinity for sst1 and sst5 than octreotide or lanreotide.[8]

The multi-receptor binding profile of pasireotide may have the potential to be effective not only in patients with acromegaly or NETs who respond to octreotide or lanreotide but also in patients unresponsive or refractory to these agents, as well as in other diseases associated with sstr expression other than sstr2. As ~90% of GH-secreting pituitary tumours express sstr2 and sstr5, octreotide and lanreotide have been used to treat acromegaly successfully. However, given that pasireotide has ~40-fold higher affinity and a 158-fold higher functional activity for sstr5 than octreotide, pasireotide may be more effective than octreotide in acromegaly treatment.[95] In phase II clinical trials, pasireotide has been demonstrated to inhibit GH secretion from pituitary tumours, control symptoms of the carcinoid syndrome associated with metastatic NETs and inhibit ACTH secretion in Cushing's disease.[96]

SYMPTOM AND BIOCHEMICAL RESPONSE

SST analogues have been demonstrated in numerous studies to represent the best available agents to induce symptomatic relief in patients with sstr positive, hormone producing NE tumours. SST scintigraphy, which depends on the expression of sstr (especially sstr2), has some predictive ability in determining functional response in these tumours. The symptomatology they control differs depending on tumour location and which amines/peptides are produced, but includes sweating, flushing, diarrhoea and bronchospasm.

There has been a controversy regarding the relative efficacy of octreotide and lanreotide. Most studies include both primary and secondary treatment and no stratification of the cohort before analysis. In a prospective cross-over study comparing the efficacy of octreotide and lanreotide in 33 patients with the carcinoid syndrome, no differences in symptom control or control of biochemical markers were seen.[97] Although it is generally considered that the available SST analogues have a similar efficacy in treating hormone induced NET symptoms, some differences in response may exist. In addition, it has been demonstrated that

tumours refractory to one analogue may respond to the treatment of another.[98] Pooled data of octreotide and lanreotide trials spanning the last two decades and including 476 patients reflect a mean symptomatic response rate of 73.2% (range 50–100%) (Table 2). Studies on the long-acting analogue octreotide LAR (5 studies, 125 patients) demonstrate a symptomatic response rate of 74.2% (61.9–92.8%), while the mean symptomatic response data for long-acting lanreotide is 67.5% (40.0–100%). The biochemical response rates (partial + complete response) are for octreotide 50.9% (range 28–77%), octreotide LAR 51.4% (31.5–100%) and long-acting lanreotide (10 studies, 356 patients) 39.0% (17.9–58%). A recent study comparing the biochemical response for lanreotide Autogel and lanreotide showed similar efficacy between the two formulations (59.3 and 55.2% respectively).[59] The reasons for minor differences are manifold. The tumour subtype, extent of disease, especially hepatic tumour load and degree of functionality as well as the used SSA dose, varying co-treatments (surgery, IFNs, chemotherapy, ablative techniques) and unclear endpoints, do not allow a direct comparison. In addition, different sstr expression patterns of neuroendocrine tumour tissues in small patient cohorts may be of importance for variable response rates, A Phase II, open-label, multicenter trial evaluated the efficacy and safety of pasireotide in 44 patients with metastatic GEP-NETs whose symptoms (diarrhoea and flushing) were inadequately controlled by octreotide LAR. Patients initially received pasireotide 300 μg s.c. b.d., with dose escalation allowed every 3 days up to a maximum dose of 900 μg s.c. b.d., if needed to achieve a clinical response. Preliminary results indicate that pasireotide may control symptoms of diarrhoea and flushing in up to 27% of patients with metastatic GEP-NETs refractory or resistant to octreotide LAR.[99]

Carcinoid crisis manifested by profound flushing, extreme blood pressure fluctuations, bronchoconstriction, arrhythmias and confusion or stupor lasting hours or even days may occur, especially during anaesthetic induction or an invasive radiological procedure.[100, 101] This potentially fatal syndrome can occur after manipulation of tumour masses (including bedside palpation), after administration of chemotherapy or after hepatic arterial embolization, especially in patients with extensive disease.[102] In general, SST analogues have replaced other pharmacological interventions in the treatment of crisis and their usage has resulted in increased survival rates.[103] Prophylactic use of subcutaneous octreotide and intravenous infusion is mandatory to prevent or obviate the development of a crisis.

THE EFFECT OF SST ANALOGUES ON NE CELL PROLIFERATION

Given the efficacy of octreotide and lanreotide in controlling tumour-associated symptoms, the question of the effect of higher doses on tumour growth was early evaluated.[77, 104, 105] Although it was noted that octreotide stabilized tumour growth in ~50%,[106] the results on objective tumour response were poor and the discussion of the antineoplastic properties of SST analogues *in vivo* remained controversial. Recent data derived from the PROMID Phase III study provide more substantial evidence that long-term administration of octreotide LAR inhibits tumour growth.[107] This study demonstrated that octreotide LAR more than doubled time to tumour progression in patients with well-differentiated metastatic neuroendocrine midgut tumours compared to placebo. Eighty-five treatment naïve patients were randomly assigned to 30 mg monthly octreotide LAR or placebo. Median time to progression was 14.3 months in the study arm compared with 6 months in the placebo arm (HR = 0.34; 95% CI, 0.20–0.59). After 6 months, 67% of patients in the study arm had stable disease compared with 37.2% of patients assigned to placebo, a highly significant difference. All patients in the placebo arm were progressive. The greatest benefit was achieved in individuals who had limited liver metastases, more precisely with <10% hepatic tumour load and this further emphasizes the significance of early diagnosis and initiation of therapy. The effect was independent of the functionality of the tumour.[107]

A small intestinal tumour origin of a gastrointestinal NET has been suggested as likely to predict a better tumour stabilizing response.[108] In a clinical trial with high-dose lanreotide, higher rates of tumour growth inhibition were observed in midgut tumours in contrast to foregut tumours.[9] *In vitro* assessment of SST analogues has clearly demonstrated an antiproliferative effect; nevertheless, reports on reduction in tumour size are modest in extent (0–8%) even with high dosages and information regarding complete regression is often anecdotal, not rigorous and has, to our knowledge, rarely been reported.[109] Among 12 patients with advanced and progressive midgut tumours treated with high-dose long-acting octreotide pamoate (160 mg), tumour size remained stable in

nine of the 12 patients with a median duration of 12 months. Although no significant radiological response was detected, minor tumour shrinkage could be demonstrated in five patients and at least three of eight evaluable patients had a decreased proliferation index during treatment.[110] Although there were indications that increasing the dosage of SST analogue to >3 mg/day may further induce tumour regression, it still was <10%.[111] Overall evaluation of the mean rate of stable tumour disease in the entire patient population treated with octreotide is 51.1% (15.0–100%), octreotide LAR 67.5% (40–87.5%), lanreotide 35.7% (8.0–70.0%) and long-acting lanreotide 61.6 (40.0–81.0) (Figure 3). A few trials report objective improvements in tumour size in between 3% and 8% of patients, with no clear difference between the different compounds. Overall tumour responses (stable disease + partial response) in the entire patient population treated with octreotide is 57.4% (36.5–100%), octreotide LAR 69.8% (47.0–87.5%), lanreotide 46.6 (32.0–75.0%) and long-acting lanreotide 64.4% (48.0–87.0%).

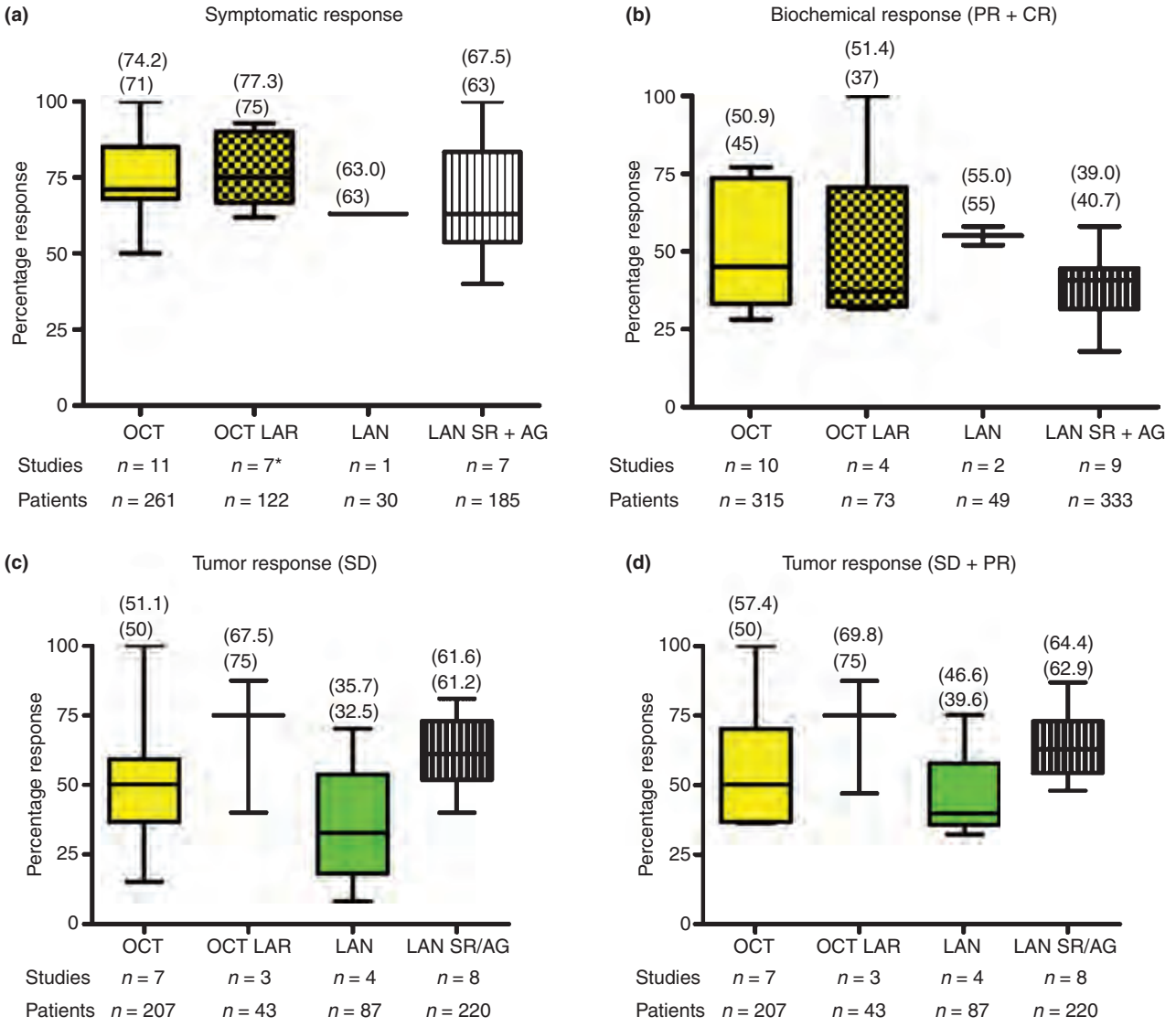

Figure 3. A compilation of the efficacy of different somatostatin analogues and different formulations. Individual numbers used are based on Table 2. (a) Symptomatic response; (b) biochemical response; (c, d) tumour response. PR, partial response; CR, complete response; SD, stable disease. Mean (top) and median in brackets. *Ref. 90 counts as $n = 3$ as they studied the response to three different doses.

A phase III study of 60 patients (46 completed the study) with well differentiated NETs treatment with lanreotide autogel (120 mg every 6 weeks) was compared to lanreotide microparticles every third week.[59] Tumour size, tumour markers and symptoms were evaluated after 18 weeks of treatment. The two regimens were indistinguishable in their effect in controlling tumour progression (67.9% and 65.5%).

STUDIES OF SST ANALOGUES IN COMBINATION WITH OTHER AGENTS

The question whether SST analogues and IFN exhibit a synergistic effect in the management of neuroendocrine tumours is controversial. The evaluation of the efficacy of combined treatment with octreotide and IFN-alpha is hampered by the small number of studies. No improved effect on tumour size compared with single agent treatment has been shown in two prospective randomized clinical trials.[9, 112] With respect to symptomatic response, both lanreotide and IFN-alpha were similarly effective in controlling the symptoms of the carcinoid syndrome, the combination of lanreotide and IFN-alpha was superior, however, associated with more frequent side effects.[9] Symptoms responded to octreotide and IFN-alpha plus octreotide without any significant differences when the drugs were used in the initial treatment of the carcinoid syndrome.[112]

Several studies, however, support the hypothesis that symptom control may be improved when IFN-alpha is added to SSAs. The overall biochemical response rate is ~75% in the available trials and is thus higher than the rates for each of the individual agents.[10, 113–116] In a randomized clinical trial with disseminated midgut tumours, patients treated with octreotide and IFN-alpha compared with octreotide alone had a significantly reduced risk of tumour progression. Nevertheless, there was no demonstrable significant difference in survival between patients treated with octreotide alone compared with combination therapy.[116]

In a phase II study of octreotide and bevacizumab (a monoclonal antibody against VEGF-A), improved progression-free survival (PFS) compared with those receiving octreotide+peg-IFN (96% vs. 69% after 18 weeks) and a higher rate of partial tumour remissions (18% vs. 0%) were demonstrated.[117] Phase II clinical studies using mTOR inhibitors in the treatment of low-grade NETs have also shown minimal (~6%) tumour response rate.[118] The activity of the oral inhibitor of mTOR, everolimus (RAD001) in combination with octreotide LAR, was recently studied in 60 patients with advanced low-to-intermediate-grade NETs.[14] There were 13 patients (22%) with partial responses, 42 (70%) with stable disease and 5 (8%) patients with progressive disease. Partial remissions were more frequent in endocrine pancreatic tumours compared with carcinoids of different primary tumour origin (27% vs. 17%). Overall median PFS was 60 weeks. Among 37 patients with elevated chromogranin A, 26 (70%) achieved normalization or more than 50% reduction. One-, two- and three-year survival rates were 83%, 81% and 78% respectively.[14] In comparison, in 2003, the overall 1-, 2- and 3-year survival rates for all GI NETs (irrespective of stage and grade) in the SEER data base were 88%, 83% and 78% respectively. The 1-year survival rates in SEER for well and intermediately differentiated NETs with distant spread, however, were only 49% and 33% respectively.[119]

CONCLUSIONS

SST analogues remain the main symptomatic therapeutic modality for the management of NETs. Generally, their effects are limited to symptom control and stabilization of the disease progress. While decrease in tumour size rarely occurs, the recent PROMID study using octreotide LAR demonstrates a clear effect on time to tumour progression compared with placebo and tumour disease stabilization. The decrease in biochemical tumour markers is evident in about 50%. Long-acting analogues have increased the duration of therapeutic control from hours up to 4 weeks. Thus, advances in drug delivery and development of more stable formulations and slow-release depot formulations have substantially facilitated symptom management and significantly improved quality of life.

When reviewing the available studies on the use of SST analogues in NET disease, we find only minor differences between octreotide LAR and lanreotide MP in controlling NET hormone release and tumour growth. Additionally, the available studies have different inclusion criteria (tumour subtype, extent of disease), various co-treatments (surgery, IFNs, chemotherapy, ablative techniques) and the end-points are not well defined and differ from study to study. The available studies are therefore more or less incomparable and a well balanced conclusion is not possible to make. Additionally, the only available study directly comparing the efficacy of two drugs in the

treatment of the carcinoid syndrome found no statistical differences.[97]

Although no additional effect of IFN in combination with octreotide or lanreotide could be demonstrated with respect to objective response rates, IFN may be of benefit in patients with carcinoid syndrome when refractory to SSA alone. First results indicate the usefulness of the panreceptor agonist pasireotide in patients with the carcinoid syndrome in patients with insufficient symptom control. The recent evaluation of the tyrosine kinase (mTOR) inhibitor, everolimus (Afinitor®) in combination with octreotide LAR appears to be an effective therapy available, with a 3-year survival rate of ~80% in patients with inoperable metastatic NET disease. The value of this treatment is currently further evaluated in clinical trials. In addition, the combination therapy of octreotide with bevacizumab is further evaluated after first results of a phase II clinical study have demonstrated promising results. In consideration of the clinical evidence of the antiproliferative efficacy of SSAs, this class of drug appears an important partner for future combination therapies, also with molecular-targeted therapies like IGF-1 receptor antibodies or sunitinib.

Even if it is now 36 years since SST was first discovered, the understanding of its biological activities is far from being fully elucidated. With modern techniques, new subtype receptor specific SST analogues and also chimeric compounds are being developed. Theoretically, these drugs have the potential to improve further the efficacy in NET treatment; their clinical utility, however, remains to be elucidated.

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