The antiproliferative effect of somatostatin analogs : clinical relevance in patients with neuroendocrine gastro-entero-pancreatic tumours

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Abstract

Somatostatin analogs (SSAs) have an important role in the management of patients with neuroendocrine tumours of the gastrointestinal tract and pancreas (GEP NETs). These compounds can control the symptoms induced by the production of hormones and peptides. The antiproliferative effects of SSAs and especially tumour shrinkage are less obvious in patients with GEP NETs than in those with acromegaly. However, based upon phase II experience there is a strong suggestion of a disease stabilizing effect of SSAs in selected patients. Those patients with a progressive, non-functional GEP NET, positive octreotide scintigraphy, a low proliferation index and in the absence of surgical options may benefit from a first-line medical therapy with SSAs. The exploration of the mechanisms of this effect are unclear and hampered by the lack of suitable preclinical models.

The better understanding of the tumour biology of GEP NETs, together with the development of new SSAs with better affinity on all somatostatin receptors, represent an unmet medical need. (Acta gastroenterol. belg., **2009**, 72, **54-58**).

Key words : neuroendocrine tumors, somatostatin analogs, antiproliferative effect.

Introduction

The treatment with somatostatin analogs (SSAs) represents a cornerstone in the management of patients with neuroendocrine tumours (NETs) of the gastrointestinal tract and pancreas (GEP) (1). The impact on symptom control by lowering hormone and peptide production is well established. The use of SSAs for their antiproliferative effect in patients with GEP NET remains a controversial topic, while it is an accepted indication in patients with acromegaly. In this overview we will mainly focus on the postulated mechanisms and observed effects of somatostatin analogs on the disease control rate (tumour stability or response) of GEP NETs.

Somatostatin and its analogs

The naturally occuring somatostatins (SSTs) are a family of peptide hormones (e.g. SST-14 and SST-28), that bind with high affinity to 5 SST cell surface receptors (SSTR1-5) (1,2). 2004). The action of SST depends on the site of formation. SSTs inhibit the secretion of growth hormone and all gastrointestinal hormones (3). In addition to the inhibition of exocrine and endocrine secretions. SSTs also influence gut motility, splanchnic flow, absorption, cell proliferation, cell survival and angiogenesis. The half-life of natural SSTs is less than 3 min in the systemic circulation, which led to the development of synthetic SSAs with longer half-lives (octreotide, lanreotide and more recently vapreotide).

All 5 SSTRs bind to the natural SSTs, with similar affinity except for the SSTR-5 which has a higher affinity for SST-28. Synthetic analogues bind mainly to SSTR-2 and SSTR-5, moderately to SSTR-3 and have a low affinity for SSTR-1 and -4. The binding affinities of SST and its analogs are given in table 1 (1). The signalling pathways that are activated through the SSTRs are complex and include inhibition of adenyl cyclase or modulation of mitogen-activated protein kinase (MAPK) through G-protein-dependent mechanisms.

Neuroendocrine tumours are a heterogenous group, which is also reflected in the expression of somatostatin receptors on the cell membrane of the tumour cells. In table 1 the expression of the different subtypes of SSTRs is summarized (1,4). The majority of GEP-NETs express SSTR-2, for which current somatostatin analogs have the highest affinity. This may explain the success of these analogs in the current treatment paradigm.

Preclinical studies on the antiproliferative effect of somatostatin analogs in GEP NET

While there is a wealth of preclinical work on SST and its analogs on pituitary cells and medullary thyroid carcinoma cell lines, there are very limited data

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Submission date : 23/12/2008
Acceptance date : 24/12/2008

Table 1. — **Expression of somatostatin receptors in GEP NET and binding affinities of somatostatin and analogs to the SSTR-subtypes (1,4)**

	SSTR-1	*SSTR-2*	*SSTR-3*	*SSTR-4*	*SSTR-5*
Expression in mid-gut NET (%)	80	95	65	35	75
Expression in pancreatic NET (%)					
a. Non-functioning	80	100	40	100	60
b. gastrinoma	33	50	17	83	50
c. VIPoma	100	100	100	100	100
d. glucagonoma	67	100	67	67	67
e. malignant insulinoma	33	100	33	100	67
Binding affinities of somatostatin and analogs (nanomoles, mean ± standard error)					
a. Natural somatostatin 14	0.93 ± 0.12	0.15 ± 0.02	0.56 ± 0.17	1.5 ± 0.4	0.29 ± 0.04
b. octreotide	280 ± 80	0.38 ± 0.08	7.1 ± 1.4	> 1000	6.3 ± 1.0
c. lanreotide	180 ± 20	0.54 ± 0.08	14 ± 9	230 ± 40	17 ± 5

regarding GEP NET. This is mainly explained because of the lack of suitable cell lines and tumour models.

SSAs have a *direct* proliferative action that is mediated through SSTRs, including activation of tyrosin phosphatases and activation of cellular cascades that stimulate growth inhibitory pathways, apoptosis and inhibit angiogenesis (5).

In addition, SSAs may exert *indirect* effects by inhibiting the release of many growth factors. As such, the presence of SSTRs (e.g. by octreotide scintigraphy) may not necessarily represent a *conditio sine qua non* for the treatment with SSAs.

In the human medullary thyroid carcinoma TT cell line, which expresses all 5 SSTRs, SST and its analogs inhibit cell proliferation via SSTR-2 (6). A decrease in cyclin D1 levels may be an important element in the SSTR2-mediated anti-proliferative effect (7).

Interestingly, it was shown in human pancreatic adenocarcinoma that cells lose the ability to express SSTR-2. Reintroducing this receptor into the pancreatic cancer cells resulted in inhibition of cell proliferation (8).

Very recently, octreotide was found to inhibit cellular proliferation in a rodent-derived insulinoma cell line, through interference with phosphorylation sites in the Akt/mTOR/p70S6K pathway (9,10). In mice xenografted with the neuroendocrine cell line BON-1, mean tumour volume decreased by 50% after 28 days of treatment with octreotide.

Clinical benefit of somatostatin analogs in patients with gastro-entero-pancreatic neuroendocrine tumors

Patients may present with clinical symptoms due to the tumoral mass or hormonal hypersecretion, the latter being the defining characteristic of a functioning neuroendocrine tumor. Nonfunctioning NETs may show positivity for peptides or amines by immunohistochemistry, but patients have no clinical symptoms due to hormone production. Due to the lack of hormonal secretion, these patients most often present with advanced disease, causing abdominal pain, weight loss or jaundice by a locally inoperable tumor or metastases (11).

The clinical benefit of any therapy may therefore be defined as *reduction of mortality and/or morbidity*, either caused by *hormonal hypersecretion* or *the tumoral mass*. So far, no prospective trial has been able to assess any survival benefit in patients treated with somatostatin analogs. However, there are certainly beneficial effects in terms of reduction in morbidity.

Control of clinical symptoms induced by hormonal hypersecretion

Somatostatin analogs have been evaluated prospectively for the control of the carcinoid syndrome in patients with the midgut NETs. Between 38% and 88% of patients experienced a marked reduction in flushing and/or diarrhea, the cardinal symptoms of the carcinoid syndrome (12-17). In one such multicentre study of 33 patients diagnosed with the carcinoid syndrome, treatment with lanreotide was compared with octreotide administration in terms of efficacy in controlling symptoms (17). Clinical benefit was seen in somewhat higher frequency with octreotide than with lanreotide (68% versus 53.8% respectively).

Similar symptom control was witnessed in patients with pancreatic NETs. In case of insulinomas – while it is not considered a first choice therapy – octreotide was effective in control of hypoglycaemia in more than 50% of 17 patients (18). SSAs may also be effective in alleviating the glucagonoma induced necrolytic migratory erythema (19,20). Octreotide administration will improve life threatening diarrhea in more than 90% of patients with a VIP producing NET (21,22). Insufficient control of symptoms by SSAs may warrant a dose increase.

In addition, therapy with SSA is generally well tolerated. Although the formation of gall stones is of concern,

Table 2. — **Results of somatostatin analogs in patients with progressive GEP NET**

Author	*Primary NET*	*Nr of patients*	*Medication*	*Stable disease*	*Regression**
Saltz (23)	Mixed	34	Octreotide	50% (2-27 months)	0
Maton (24)	Pancreatic	107	Octreotide LAR, various doses	39%	7.5%
Arnold (25)	Mixed	52	Octreotide (600-1500 μg/day)	36.5% (3-36 months)	0
Di Bartolomeo (26)	Mixed	58	Octreotide (1500-3000 μg/day)	47% (6-32 months)	3%
Erikson (27)	Mixed	13	Lanreotide (12,000 μg/day)	70% (for 12 months)	5%
Faiss (28)	Mixed	30	Lanreotide (15,000 μg/day)	36% (for 1 year)	6.7%
Aparicio (29)	Mixed	35	Various : octreotide or lanreotide	57% (6-48 months)	3
Shojamanesh (30)	Gastrinoma	15	Octreotide LAR (20-30 mg/month)	47% (25 ± 6 months)	6%**
Arnold (31)	Mixed	52	Octreotide	At 3 months : 44.8% At 6 months : 27.6% At 1 year : 15.2%	2.9% 1.9% 5.7 %

* Variable criteria (most often > 50% reduction in diameter) ; ** > 25% reduction in diameter.

this is rarely (< 1% of patients) symptomatic (1). Therefore, the treatment with somatostatin analogs represents an accepted indication in patients with clinical symptoms due to hormonal hypersecretion.

Control of tumor growth

The ideal study to demonstrate an antiproliferative affect would consist of a randomized controlled trial in patients with NETs, using modern evaluation of response by RECIST criteria and stratified for proliferation index (e.g. Ki67), primary location (pancreatic *versus* midgut NET) and the presence/ absence of a functional syndrome. Ongoing phase III trials will hopefully answer this important question. The results of the PROMID trial that randomized patients with midgut NETs to octreotide or placebo are pending.

Up to now, only phase II studies suggest a tumour-stabilizing effect of these compounds. Especially trials that included patients with documented tumour progression only, allow to look at stable disease as a proof of activity (23-31). These trials are summarized in table 2. When reported, objective response rates are less than 10% (0-7.5%), whereas stable disease is seen in 31.6-70% of treated patients for 2-36 months.

We also included in the analysis the control group of the randomized trial of Arnold (31), who evaluated the effect of octreotide and interferon *versus* octreotide alone. This study did not show a benefit of the combination, but clearly highlighted the disease stabilizing effect of octreotide in progressive tumors at the time of inclusion. The variability in efficacy between the phase II trials may be due to the inclusion of patients with unfavourable tumour biology (high proliferation index). Moreover, those studies that used higher than the usual dose of SSAs seemed to yield better results (27,28). It may very well be that higher doses of octreotide exert more profound effects with a demonstrated excellent safety profile when given 60 mg per month. Interestingly, in some studies it appeared that patients with slow-growing tumours were more likely to respond to SSAs (29,30). In addition to phase II studies, there is a wealth of case reports suggesting an anti-proliferative effect of SSAs. In a case report of a patient with multiple type 1 gastric NETs, treatment with octreotide LAR (long acting release) for 9 months led to normalisation of serum gastrin levels and disappearance of the tumors (32). In 5 patients with hypergastrinemia and gastric NETs, octreotide LAR during 1 year resulted in a significant reduction in tumour load and normalisation of circulating chromogranin A levels (33).

Based upon these data, there is a sound rationale to advocate SSA therapy as first-line medical therapy outside clinical trials in patients with well differentiated, non-functional GEP NET, provided the documentation of tumour progression, a low proliferation index (< 5%), a positive somatostatin receptor scintigraphy and the absence of surgical options (11). In case of documented, progressive disease during an adequately dosed SSA therapy, SSAs should be withdrawn.

Research agenda

We need a better understanding of the tumour biology, the development of preclinical models and new SST analogs. Pasireotide is a new and promising SSA, having a high affinity for SSTR-1, SSTR-2, SSTR-3 and SSTR-5. Pasireotide has a 30-40 times higher affinity for SSTR1 and SSTR5 than octreotide (34). The compound is under evaluation in phase I-III trials, comparing pasireotide with octreotide LAR and in octreotide-refractory patients (35,36). Preliminary data suggested that at least some of the refractoriness of NETs to octreotide may be due to the expression of SSTRs other than SSTR-2. It remains to be determined whether this SSA may have a significant antiproliferative effect.

In addition to pasireotide, chimeric analogs that bind to SSTRs and dopamine-2 receptors, have been developed (37).

Summary

SSAs have an important role in the therapeutic algorithm of patients with GEP NETs, by their ability to control symptoms induced by hormonal secretion. The literature regarding the anti-proliferative mechanisms of SSAs and their role in the treatment of NETs is heterogeneous and the analysis poses a great challenge. The existing phase II studies of SSAs in selected patients with GEP-NETs indicate a disease stabilization under these compounds. Results of phase III studies are pending.

Based upon these data and experience outside clinical trials, there is a sound rationale to advocate SSA therapy as first-line medical therapy in patients with well differentiated non-functional GEP NET, provided the documentation of tumour progression, a low proliferation index (< 5%), a positive octreotide scintigraphy and the absence of surgical options. The better understanding of the tumour biology of GEP NETs, together with the development of new SSAs with better affinity on all somatostatin receptors, represent important challenges for the future.

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