Symposium article

Summing up 15 years of somatostatin analog therapy in neuroendocrine tumors: Future outlook

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Summary

Neuroendocrine gastrointestinal tumors express somatostatin receptors (ssts) in 80%–90% of cases and somatostatin analogs have become increasingly important in the management of these patients. Most of the presently available somatostatin analogs (octreotide, RC-160, and lanreotide) bind to the sst2 and sst5, and in higher doses to sst3 of the ssts 1–5 described.

Clinical improvement during somatostatin analog therapy is mainly mediated via a direct inhibitory effect on hormone production from the tumors, seen in 30%–70% of the patients. Also indirect non-tumor mediated effects on peripheral target organs contribute to the subjective improvement, achieved in 30%–70% of patients. Recently, significant improvement of quality of life has been demonstrated with long-acting depot formulations. There is little or no effect on tumor growth during octreotide therapy; tumor shrinkage has been reported in 10%–20% of patients, but stabilization of tumor growth can be achieved in about half of the patients with a duration of 8–16 months. Recently, induction of apoptosis has been described with high doses of lanreotide (12 mg/d). Eventually, however, all patients escape from somatostatin analog therapy with regard both to hormonal production and tumor growth, and the mechanism behind the tachyphylaxis is not yet known.

Studies of optimal dosage and modes of administration, development of new slow release formulations, the potential value of high-dose somatostatin analog therapy and novel somatostatin receptor subtype specific analogs are important directions for the use of somatostatin analogs in the future. In addition, assessment of somatostatin receptor status for each patient and studies of tumor biology, e.g., inhibition of exocytosis, antiproliferative effects and induction of apoptosis during treatment will help to optimize treatment and provide new insights into mechanisms of action of somatostatin analogs.

Key words: apoptosis, lanreotide treatment, neuroendocrine gastrointestinal tumors, octreotide, somatostatin analogs

Introduction

Neuroendocrine gastrointestinal tumors usually present with metastatic inoperable disease and more or less severe hormonal symptoms [1, 2]. A multimodal approach is then warranted and the aims of treatment is to control hormonal symptoms, reduce circulating hormone levels, prevent further tumor growth and possibly also achieve tumor reduction, stop progression of carcinoid heart disease, prolong survival and improve quality of life. Chemotherapy, i.e., combinations with streptozocin, can produce objective responses in endocrine pancreatic tumors (EPT) but is of little benefit in carcinoid tumors [3, 4]. Alpha-interferon (IFN) has been used in both EPTs and carcinoids with responses in 40%–50% of patients [5, 6]. Liver embolizations can produce biochemical and tumoral responses of varying durations [7, 8]. However, very few patients are cured by any of these therapies and hence, there is a need for other therapeutic options.

Somatostatin analogs, octreotide being the first analog available for clinical use, have become increasingly important in the management of these patients. The rationale for the effect of these agents has been elucidated by the demonstration of somatostatin receptors in 80%–90% of tumors by autoradiography [9] and octreotide scintigraphy [10], the latter method having emerged as a routine diagnostic tool for staging of the patients, and also as a predictive test for sensitivity to treatment with somatostatin analogs [11]. Most of the somatostatin analogs presently available for clinical use (octreotide, lanreotide, RC-160) bind with high affinity to somatostatin receptors sst2 and sst5, and with lower affinity to sst3 [12], of the ssts 1–5 described [13–16].

The beneficial effects of native somatostatin in blocking the carcinoid flush induced by pentagastrin, reducing circulating levels of serotonin and controlling other symptoms associated with the carcinoid syndrome were described by Thulin et al. and Fröhlich et al. in 1978 [17, 18]. However, the clinical use of native somatostatin was hampered by its short half life of only two minutes, which necessitated continuous intravenous infusion, and rebound phenomena that occurred after withdrawal of infusion. In 1982, Bauer et al. reported on the synthesis of the long-acting octapeptide analog, octreotide (or SMS 201-995), which retained the four amino acid sequence presumed to be essential for biological activity and was cyclized with a disulfide bridge to impair degra-
conducted over the last 10 years in patients with metastatic neuro-endocrine tumors. See Refs. [49, 53, 54].

d See Refs. [22, 34-37, 39-43].

Response
carcinoid/hormonal crises and perioperative situations, short-term clinic and the or acute use of the drug in subcutaneously two to three times daily [19].

d See Refs. [59-61].

n Radiological, (%)

Table 1. Symptomatic (subjective), biochemical and radiological responses to different treatments with somatostatin analogs in studies conducted over the last 10 years in patients with metastatic neuro-endocrine tumors.

<table>
<thead>
<tr>
<th>Response</th>
<th>Standard doses of octreotide (100-1500 μg/d)</th>
<th>Slow release lanreotide (30 mg/14 day i.m.)</th>
<th>High dose lanreotide (9-15 mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic, n (%)</td>
<td>146/228 (64)</td>
<td>34/66 (52)</td>
<td>11/26 (42)</td>
</tr>
<tr>
<td>Biochemical, n (%)</td>
<td>6/54 (11)</td>
<td>2/80 (2.5)</td>
<td>1/33 (3)</td>
</tr>
<tr>
<td>CR</td>
<td>116/211 (55)</td>
<td>35/80 (44)</td>
<td>24/33 (72)</td>
</tr>
<tr>
<td>PR</td>
<td>NS</td>
<td>32/80 (40)</td>
<td>7/33 (21)</td>
</tr>
<tr>
<td>SD</td>
<td>NS</td>
<td>11/30 (35)</td>
<td>1/33 (3)</td>
</tr>
<tr>
<td>PD</td>
<td>74/131 (56)</td>
<td>8/42 (19)</td>
<td>21/53 (39)</td>
</tr>
<tr>
<td>Radiological, n (%)</td>
<td>-</td>
<td>-</td>
<td>1/53 (2)</td>
</tr>
<tr>
<td>CR</td>
<td>7/131 (5)</td>
<td>2/42 (5)</td>
<td>6/53 (11)</td>
</tr>
<tr>
<td>PR</td>
<td>50/131 (38)</td>
<td>32/42 (76)</td>
<td>25/53 (47)</td>
</tr>
<tr>
<td>SD</td>
<td>74/131 (56)</td>
<td>8/42 (19)</td>
<td>21/53 (39)</td>
</tr>
</tbody>
</table>

Endocrine pancreatic tumors

Insulinomas
When octreotide (50 μg twice a day) was given preoperatively, it had inconsistent effects on insulin and glucose levels [25]. In some patients possibly because of more profound suppression of GH and glucagon than tumor-produced insulin, the hypoglycemia was worsened. Patients with metastatic insulinomas given octreotide over long-term improved symptomatically and biochemically in 50% of cases [26]. We now know that 50% of insulinomas lack expression of sst2 [27], thought to predominantly mediate the biochemical response [28], which explains the absence of effect in 50% of insulinomas.

Gastrinomas
More than 50 patients with gastrinomas have been treated with doses of 100–1,500 μg/d, most of them short-term. Of these, 90% had a good clinical response with control of gastric hypersecretion, pain and diarrhea. A significant drop in serum gastrin and basal acid secretion was obtained [25]. In a long-term study, Ruszniewski et al. could show that also maximal acid output decreased during 9–12 months of treatment, suggesting an antitrophic effect (i.e., reduction of parietal cell mass) of octreotide [29]. The efficacy of octreotide in lowering the number of antral G-cells and its effect on long-lasting hypergastrinemia (i.e., ECL cell hyperplasia) are currently being evaluated. However, octreotide has an undefined role in gastrinomas because of the efficient and more convenient peroral proton pump inhibitors. With the recent development of slow release formulations of somatostatin analogs, there may be subgroups of malignant gastrinomas that could benefit from this treatment.

VIP-omas
In patients with VIP-omas not curable by surgery and in whom chemotheraphy is only transiently useful, octreotide is now the treatment of choice. Symtomatic improvement occurs in > 80% of patients at doses of 100–450 μg/d. However, in some patients the beneficial effect lasted only a few days requiring increases in dose [25]. Biochemical responses could be noted in about 80% of patients. Symtomatic relief was not always related to the reduction in plasma concentrations of VIP, indicating that octreotide has a direct effect on the gut. In some cases octreo-
response is independent of plasma glucagon concentrations, suggesting a direct effect of octreotide on the skin. Also in glucagonomas, octreotide can change circulating molecular forms of glucagon, indicating inhibition of posttranslational processing of preproglucagon, thereby reducing circulating bioactive glucagon [31].

**Somatostatinomas**

A small number of patients with somatostatinomas have been treated with octreotide and they improved symptomatically and biochemically, which correlated with the presence of somatostatin receptors in the tumors evidenced by octreotide scintigraphy [32].

The effect on tumor growth in EPT treated with standard doses of octreotide was reported by Maton in his meta-analysis although the degree or percentage of regression (e.g., 50%) was not indicated [25]. Regression was obtained in 8 of 46 patients (17%), no change in 18 of 46 (39%) and progression in 20 of 46 (44%).

**Meta-analysis of dose titration data**

Harris and Redfern performed a meta-analysis of data compiled from 62 published studies to examine the relationship between octreotide dose and efficacy in decreasing urinary 5-HIAA, flushing and diarrhea and defined dosing recommendation for maximum therapeutic benefit [33]. Six dose ranges of octreotide were assessed from 100–3,000 μg/d. Patients had to show a reduction in diarrhea, flushing, or 5-HIAA levels of greater than 50% to be included. Reduced U-5-HIAA tended to maximize as the daily octreotide dose increased and maximum response in U-5-HIAA tended to occur over the octreotide dose range of 300–375 μg/d. Increasing doses of octreotide were associated with symptom improvement: a reduction in diarrhea occurred over the dose ranges 100–1000 μg/d, with no additional benefit seen with doses over 1000 μg/d, and octreotide dose ranges from 100 to 2000–3000 μg/d resulted in resolution of flush. So they concluded, that symptom relief and reduced U-5-HIAA levels occurred in a greater percentage with increasing doses. Since the response to octreotide varies markedly among individual patients – possibly attributable to patient-to-patient variations in the relative abundance of high- and low-affinity somatostatin receptors expressed on the tumor cell membrane – it is important to titrate the dose of octreotide in each patient until adequate symptom and biochemical control is achieved.

**Antiproliferative effects**

The antiproliferative effect of standard doses of octreotide was further studied by two groups (Saltz et al., 1993 and Arnold et al., 1995) [34, 35]. Saltz et al. treated 34 patients with advanced neuroendocrine tumors, 20 previously untreated, with octreotide at doses of 150–250
three times a day first when tumor progression (> 25% over two to four months) was documented. They achieved CT-verified stabilization in 50% of patients with a median duration of five months. In a German multicentre study, 52 patients with CT-documented tumor progression were treated with octreotide 200 μg three times a day. A stabilization of tumor growth was achieved in 19 of 52 (36.5%) with a median duration of 18 months. Even though reduction in tumor size is rarely seen with standard octreotide treatment of neuroendocrine tumors, these results suggest that octreotide has an antiproliferative effect.

Summary of standard octreotide treatment
Summarizing results reported in the literature up till now [21–26, 30–32, 34–43], treatment of patients with...
neuroendocrine gastrointestinal tumors with subcutaneous injections of standard doses of octreotide produces symptomatic or subjective responses in 30%-75% of patients and the response rate appears to dose dependent. Biochemical responses are achieved in 30%-60% of patients and according to Harris' analysis, biochemical responses are also dose dependent, i.e., the dose should be titrated for each patient. More than 50% reduction in tumor size occurs only in 10%-15%, but stabilization can be achieved in 35%-50% of patients. Whether the antitumoral response is dose dependent or not will be discussed. Several in vitro studies indicate that the antiproliferative effect is dose-related [44, 45]. Both the biochemical and the antiproliferative effect of octreotide are considered to be mediated by sst2, the latter via stimulation of tyrosine phosphatase. Octreotide also binds to sst5, which mediates an antitumor response through a different mechanism, probably via calcium fluxes [46]. Occasionally, tumor growth may continue despite ongoing anti-secretory effects, suggesting these actions may be mediated by distinct mechanisms. Since sst2 mediates both biochemical and antiproliferative effects of octreotide, it is important to perform octreotide scintigraphy and possibly also assessment of the sst2 receptor status as predictive tests before initiation of treatment.

Several direct or indirect mechanisms of growth inhibitory activity of octreotide and analogs have been suggested [27]: 1) suppression of the release of trophic hormones (e.g., GH, insulin, prolactin, gut peptides), 2) direct or indirect inhibition of growth factors (e.g., EGF, PDGF), 3) inhibition of angiogenesis, 4) modulation of immunological activity, and 5) direct antimitotic effects via somatostatin receptors on tumor cells.

**Adverse effects**

The adverse effects of standard octreotide treatment have been rather mild due to the adaptation of normal pituitary and gastrointestinal functions to the drug. Apart from nausea, transient abdominal cramps, flatulence, diarrhea and local reaction at the injection site, no important side effects have been observed. Most side effects resolve with time. Octreotide also causes a short-term inhibition and/or delay of insulin release in response to meals, but this is only accompanied by a slight decrease in glucose tolerance in some patients, without notable changes in glycosylated hemoglobin (HbA1c). In 20%-50% of patients gallstones are formed de novo, but these remain virtually always asymptomatic [47]. More rare adverse events include hypocalcemia, bradycardia, acute pancreatitis and transitory ischemic attacks (the latter with high-dose in a predisposed patient).

**Tachyphylaxis**

The median duration of response to standard octreotide treatment is 12 months. Loss of therapeutic response during chronic octreotide therapy is a well-recognized phenomenon [24]. It generally conforms to one or two patterns, both of which have been ascribed altered receptor function: early (down-regulation of ssts, restorable by drug-free interval) and eventual escape (development of receptor-negative clones?). The mechanism for tachyphylaxis is not known. It does not occur, when acromegalic patients are treated with octreotide [48], so there is a fundamental tumor biological difference between these two diseases, which remains to be elucidated.

**High-dose treatment**

Very few studies have addressed the potential value of high-dose somatostatin analog treatment in neuroendocrine gastrointestinal tumors. It should be interesting, since a dose-related tumor response has been demonstrated in a variety of tumor models. So far three studies have been reported. In a study performed by our group in 1992–1993, we treated 19 patients with advanced neuroendocrine GI-tumors (13 carcinoids and six EPT) with a mean duration of disease of 56.7 months and 19 months, respectively, all except four heavily pretreated, nine failing on standard doses of octreotide [49]. Octreotide scintigraphy was positive in 17 of 18 patients before initiation of lanreotide in escalating doses up to 12 mg/d, a dose, which was maintained for one year or until progression. Biochemical responses were achieved in 11 of 19 patients (58%). One patient (5%) showed a partial tumor response, whereas stabilization was obtained in 12 of 19 (70%). We made an interesting observation in tumor biopsies from the patients. Patients with a biochemical response and stable tumor disease showed an increase in the number of apoptotic cells in the tumors with time (six and 12 months) [50] and we suggest that high-dose lanreotide may have induced apoptosis by binding to sst3 as has recently been described [51]. We also made an interesting observation using in vivo PET: in two biochemically responding patients, the uptake of the tracer L-DOPA increased, indicating inhibition of exocytosis (more than synthesis) of peptides and amines by high-dose somatostatin analogs [52]. The frequency of gallstones in this study was 1 of 19 (5%).

Anthony et al. treated 13 patients refractory to standard doses of octreotide with octreotide 6 mg/d and achieved a partial tumor response in 4 of 13 (31%) and a stabilization in 2 of 13 (15%) [53]. In the same report high-dose lanreotide (9 mg/d) was given to 13 patients with mixed diagnoses, e.g., SCLC. Among six midgut carcinoid, three obtained a partial tumor response. Faiss et al. treated 30 patients with metastatic neuroendocrine GI-tumors with 15 mg/d lanreotide for one year [54]. One complete and one partial tumor response was achieved. So, it appears that high-dose octreotide/lanreotide can produce additional antiproliferative effects in patients failing on standard doses of octreotide.
Continuous infusion

Several studies in acromegaly have indicated that continuous infusion of octreotide has advantages over intermittent subcutaneous injections; one can achieve a more pronounced control of growth hormone (GH) and insulin-like growth factors (IGF-1) levels, clinical and biochemical control can be achieved at lower doses and the adverse effects may be less [55]. To explore this, we performed a European multicentre trial treating 35 patients with the carcinoid syndrome (19 had failed standard doses of octreotide) with RC-160 at a dose 1.5 mg/d given as a continuous subcutaneous infusion via micropump for three to six months [56]. This is the first clinical study, in which RC-160 has been used and it was of particular interest, since in vitro studies have suggested that RC-160 has a stronger antiproliferative effect than both octreotide and lanreotide [57]. In brief, subjective improvement occurred in about 60%, the biochemical response rate was rather low, only 23% and there was no tumor response but stabilization was achieved in 60% in these advanced cases, which might be considered a response. The frequency of gallstones was 8%. However, the most striking observation in this study was the absence of side-effects: there were no gastrointestinal side-effects with the exception of gallstones, so the treatment was very well tolerated.

Slow release formulations

One of the most important improvements in somatostatin analog treatment is the development of slow release formulations, which relieves the patients of the inconvenience of taking multiple daily injections. Available for clinical use are now Sandostatin-LAR and lanreotide-PR, in which octreotide and lanreotide have been incorporated into microspheres of the biodegradable polymer poly (LD-lactide-coglycolide glucose), which can be given every fourth and second week, respectively. There are already reports about the beneficial value of these formulations in acromegaly and Sandostatin-LAR is expected to become the treatment of choice in acromegaly [58].

There are three reports on the use of lanreotide-PR in neuroendocrine gastrointestinal tumors. Ruszniewski et al. treated 39 patients with carcinoids with lanreotide-PR 30 mg i.m. every two weeks [59]. They found subjective responses in about 55%, biochemical responses in 42% but no tumor response after six months of treatment. The frequency of gallstones was 5%. Somewhat higher subjective (73%) and biochemical (55%) response rates were obtained in a German study including eleven patients [60]. Our group participated in a European multicentre study together with centres in Finland, Norway, The Netherlands and Belgium and treated 55 patients (48 carcinoids and seven EPT) with lanreotide-PR 30 mg i.m. every two weeks for six months [61]. Symptomatic improvement was observed in 38% of carcinoids, 67% of gastrinomas and 1 VIP-oma. Biochemical responses were obtained in 47% and tumor responses in two patients (7%), stabilization of tumor growth was achieved in 80%. Side effects were pain and flatulence the first days two to three days after intramuscular injection. The frequency of gallstones was rather high of 8 of 30 (27%). During this trial quality of life was studied using a validated EORTC instrument (C30) and assessment after 1 month showed improvements of emotional and cognitive function, global health as well as sleeping disorders and diarrhea. This is the first study that can show that a long-acting somatostatin analog improves quality of life, which is very important since the treatment is palliative.

Combination of IFN plus octreotide

The combination of somatostatin analogs with other drug is also an interesting area for the future. We have already shown that the combination of octreotide plus IFN produces a higher biochemical response rate than either drug alone in carcinoid tumors [62], we have similar indications in endocrine pancreatic tumors in our institution and a German study will soon disclose whether the combination is better than any of the single drugs in a randomised study. In vitro studies from our group indicate that the combination has a stronger antiproliferative effect than IFN or octreotide alone [50].

Conclusion

In summary, somatostatin analogs can relieve symptoms, reduce circulating hormone levels and stabilize tumor growth in >50% of patients. Whether somatostatin analogs can stop the progression of carcinoid heart disease is not known but we are currently looking at it and our general impression is that we have less problems with cardiac disease now than 10–15 years ago. There is no published study that can prove that somatostatin analogs improve survival as yet. The age at diagnosis has not been reduced despite improved diagnostic methods because of the rarity of the disease, so the better survival rates that appear in reports published recently compared to historical controls should reflect improvement in therapeutic procedures. Moreover, the majority of centres working with these patients use a multimodal approach so it is very unlikely that a patient will receive a somatostatin analog as the only treatment during the clinical course of the disease, and hence, it will be very difficult to say that this individual treatment produced a better survival. The important fact is that survival rates are improving and that as we have shown the quality of life is also improved, which is very important for a palliative treatment.
Future perspectives

The future in the area of somatostatin analogs is promising. It is important 1) to explore the clinical usefulness of slow release formulations, possibly also high-dose slow release formulations, 2) to further investigate the potential value of high-dose analog treatment and the possible induction of apoptosis, 3) to study the combination of somatostatin analogs with other drugs (IFN, chemotherapy). 4) Furthermore, somatostatin analogs can be coupled to chemotherapeutic drugs based on the observation of internalization, and the most promising field is 5) receptor subtype-specific analogs and combinations of them. There are already interesting in vitro data in pituitary tumors treated with combinations of subtype-selective analogs indicating additive or synergistic effects of combinations [63].

In the future, therapy with somatostatin analogs should be based on the sst-status of the tumors in addition to other clinical and tumor biological parameters of the patients to tailor-make treatment for each patient to possibly achieve higher symptomatic and biochemical response rates and more pronounced antiproliferative effects.

Acknowledgements

This work was supported by the Swedish Cancer Research Foundation.

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