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Somatostatin Analog Therapy in Treatment of Gastrointestinal Disorders and Tumors

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Long-acting octapeptide somatostatin analogs can effectively control symptoms resulting from excessive hormone release in patients with endocrine tumors of the gastrointestinal tract, provided that these tumors and metastases show a high expression of the somatostatin receptor subtype 2. The presence of this receptor subtype on these tumors can be demonstrated by in vitro studies, but also in vivo using ^{111}In-pentetreotide scintigraphy. In a few studies, significant antiproliferative effects of these drugs on these tumors have also been demonstrated. The effectiveness of octapeptide somatostatin analogs in the management of chemotherapy-related and AIDS-related diarrhea and in reducing postoperative complications of pancreatic surgery have also been demonstrated. These drugs have been used to decrease the output of enterocutaneous pancreatic fistulas and are prophylactically used to prevent the development of these fistulas. Octapeptide somatostatin analog therapy is widely accepted for the initial management of acute variceal bleeding in cirrhotic patients. These drugs are currently also being evaluated for the treatment of advanced hepatocellular carcinoma and malignant intestinal obstruction. Radiotherapy with octapeptide somatostatin analogs coupled to radionuclides such as indium-111, yttrium-90, and lutetium-177 is currently being studied in phase I–III trials.

Key Words: Carcinoids; gastrointestinal tract; endocrine tumor; somatostatin; analog.

Introduction

Carcinoids of the digestive tract and bronchi, and pancreatic islet cell tumors, have been classified by international expert pathologists on behalf of the World Health Organization as endocrine tumors of the gastrointestinal (GI) tract *(1)*. These tumors are very heterogeneous and show a great variability in clinical behavior. They are generally subdivided into those presenting with hormonal or hormone-related symptoms/syndromes and those without hormonal symptoms, the so-called nonfunctioning tumors. Functioning pancreatic islet cell tumors have been traditionally named according to the hormone(s) that is secreted, such as gastrinomas, glucagonomas, vasoactive intestinal peptide (VIP)omas, insulinomas, and somatostatinomas. Morbidity and mortality in patients with hormone-producing endocrine tumors of the GI tract result from either hormonal or hormone-related symptoms/syndromes, or from tumor expansion and spread. In patients with nonfunctioning tumors, morbidity and mortality mainly result from tumor expansion and spread, although these tumors may later in their disease course start producing biologically active hormones. Pancreatic islet cell tumors may occur sporadically, or as part of genetically determined autosomal dominant inherited syndromes of the multiple endocrine neoplasia type I syndrome (MIM 131100) or von Hippel–Lindau syndrome (MIM 193300) and the neurofibromatosis-pheochromocytoma-duodenal carcinoid syndrome (MIM 162240).

The first aim of treatment in a patient with an endocrine tumor of the GI tract is the control of hormone-mediated symptoms and the second is the control of tumor growth. If feasible, curative surgical removal of the primary tumor and its locoregional metastases is generally considered the first-line therapy. However, even in metastatic disease, surgical tumor debulking can be sometimes useful in the treatment of hormone-mediated symptoms and improvement of the patient's long-term prognosis.

Somatostatin Receptor Subtype Expression by Endocrine Tumors of GI Tract and Its Clinical Implications

The presence of somatostatin receptor (SSTR) subtypes on tissues or tumors can be demonstrated in vitro by various techniques, including *in situ* hybridization, Northern blotting, ribonuclease protection assays, and reverse transcriptase polymerase chain reaction. In endocrine tumors of the GI tract, there is a heterogeneous expression of the human sst subtypes. In general, there is predominant expression of the subtypes SSTR1 and SSTR2 and little to variable expression of SSTR3 and SSTR4. The efficacy of the

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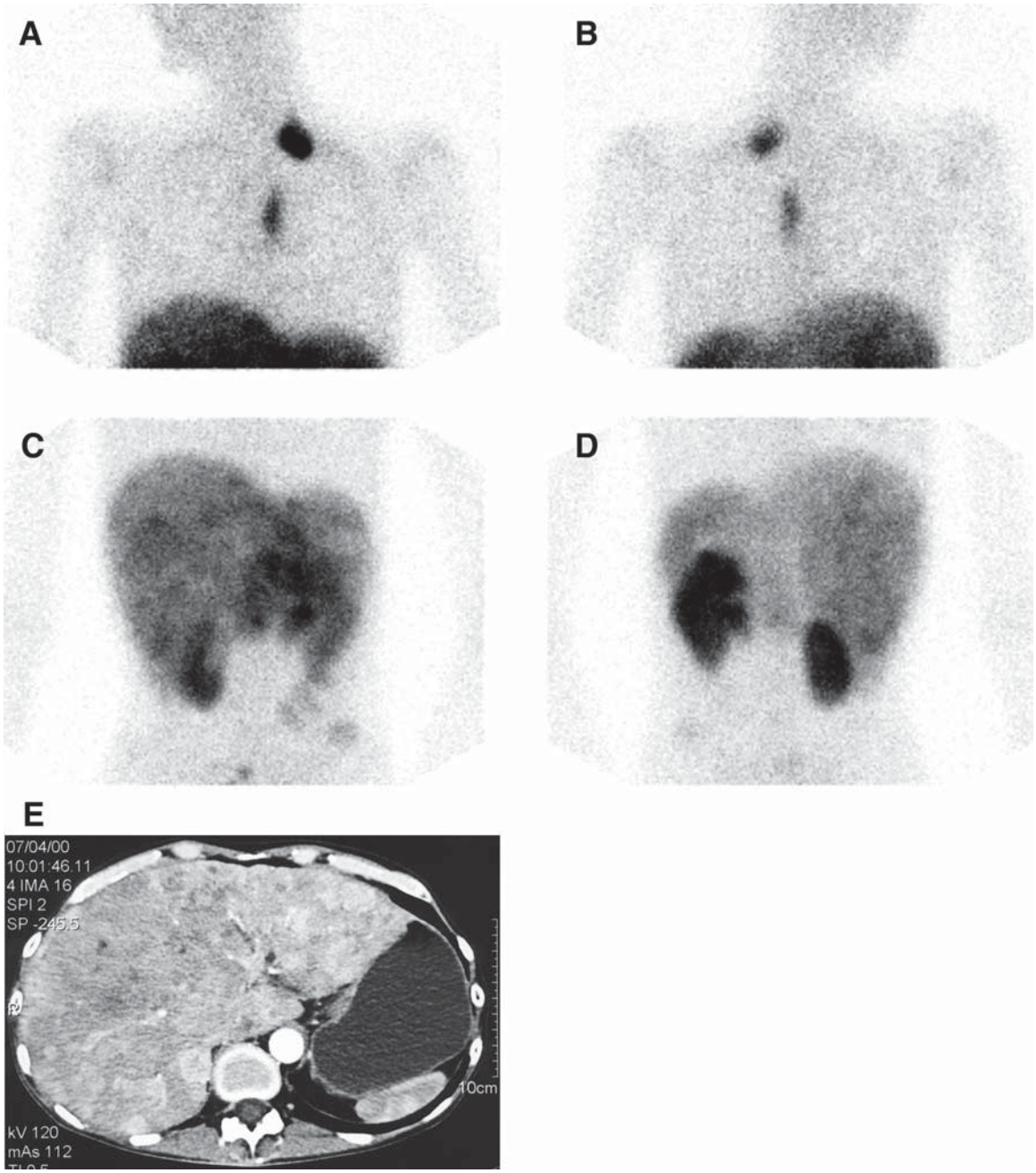

Fig. 1. (**A–D**) OctreoScan pictures obtained 24 h after injection of 225 MBq of ^{111}In-pentetreotide in a 44-yr-old male patient with a metastatic pancreatic gastrinoma and Cushing syndrome caused by ectopic ACTH secretion. (A) Planar anterior and (B) posterior images of chest and neck area showing pathologic uptake of radioligand in left supraclavicular lymph node metastasis (Virchow's node) and in mediastinal lymph node metastases. (C) Planar anterior and (D) posterior images of abdomen showing pathologic uptake of radioligand in liver metastases and in primary tumor in pancreatic head. (**E**) Transverse computed tomography image showing diffuse liver metastases.

octapeptide somatostatin analogs (octreotide and lanreotide) is mainly determined by the expression of SSTR2 on these tumors. Tumors and metastases, which bear receptors for octapeptide somatostatin analogs, can be visualized in vivo using gamma camera pictures obtained after injection of ^{111}In-pentetreotide (OctreoScan®) *(2–4)*. The technique of ^{111}In-pentetreotide scintigraphy has successively been applied successfully to patients with endocrine tumors of the GI tract *(5–8)*. In a large European multicenter trial, a total of 350 patients with islet cell tumors and carcinoids were studied by means of this technique. ^{111}In-pentetreotide scintigraphy was positive in 87% of carcinoids (n = 184), 73% of gastrinomas and nonsecreting islet cell tumors (n = 49 and n = 49, respectively), 46% of insulinomas (n = 24), 88% of VIPomas (n = 8), all five glucagonomas, and none of five somatostatinomas *(5,9,10)* (Fig. 1).

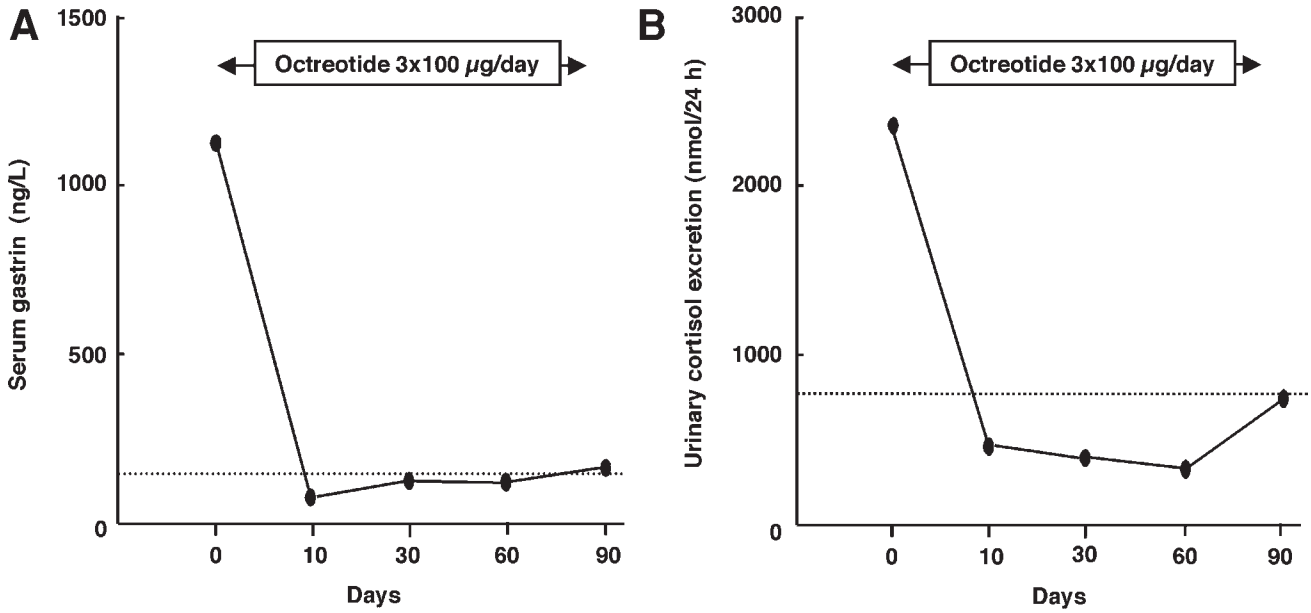

Fig. 2. Course of serum gastrin levels (**A**) and urinary cortisol excretion (**B**) in same patient as in Fig. 1 after administration of octreotide (100 µg three times daily) showing normalization of serum gastrin levels and urinary cortisol excretion for 3 mo. The patient "escaped" from this therapy after this period, despite increasing the dosage.

In prospective studies, the equipotency of the long-acting im depot formulations Sandostatin LAR, Lanreotide-PR, or the long-acting sc depot formulation Lanreotide Autogel with the short-acting sc products octreotide (Sandostatin) or lanreotide, which have to be administered via the sc (or iv) route, has been demonstrated in patients with carcinoid syndrome *(11)*.

Carcinoids of the small intestine (previously designated as midgut carcinoids) are the most common carcinoids. After metastasizing to the liver, bioactive amines may reach the systemic circulation and the carcinoid syndrome ensues. These small intestinal carcinoids account for 75–90% of all cases of carcinoid syndrome *(12,13)*. In the case of the carcinoid syndrome, octapeptide somatostatin analog therapy results in complete disappearance of flushing episodes in approx 60% of patients, while in more than 85% the frequency and/or severity of the flushing periods can be reduced to <50%. Disappearance of diarrhea is observed in more than 30%, and more than 50% improvement in more than 75% of patients with this therapy. Biochemically, a significant reduction in the increased urinary excretion of 5-hydroxy indole acetic acid in more than 50% of patients has been found *(13–17)*. However, insensitivity (tachyphylaxis) to octapeptide somatostatin analogs may develop in time *(18)*.

Octapeptide somatostatin analogs are of great value in the treatment and prevention of carcinoid crisis *(19,20)*. They must, therefore, be administered perioperatively and during laparotomy or during and shortly after invasive measures such as embolization of liver metastases, and coronary angiography in patients with metastatic carcinoids (and especially in those with the carcinoid syndrome) *(21–24)*. Their effects on carcinoid heart disease and its progression have not been clearly demonstrated *(25)*. Octapeptide somatostatin analogs control flushing, diarrhea, and hypokalemia in the Verner-Morrison (VIPoma) syndrome *(26–30)* and the necrolytic migratory erythema in the glucagonoma syndrome *(31–35)*. Octapeptide somatostatin analogs are of limited use in insulinoma patients because a major part (approx 40–60%) of the insulinomas do not express the essential SSTR subtypes (SSTR2, SSTR3, and SSTR5) needed for binding these drugs. Octapeptide somatostatin analogs effectively suppress gastric acid secretion in patients with Zollinger-Ellison syndrome by a direct effect on the parietal cells and by inhibiting gastrin release from the tumor cell *(36)* (Fig. 2A).

These drugs also have proven efficacy in some of the so-called ectopic hormone syndromes. In patients with the ectopic corticotropin (adrenocorticotropic hormone [ACTH]) syndrome, octapeptide somatostatin analog therapy results in a reduction in ACTH levels in many patients *(37,38)* (Fig. 2B). However, the unpredictable response, as well as the generally incomplete normalization of ectopic ACTH overproduction to octapeptide somatostatin analogs, generally necessitates early laparoscopic biadrenalectomy in these generally severely ill patients. Similarly, in ectopic acromegaly, caused by growth hormone–releasing hormone (GHRH) production by neuroendocrine tumors, octapeptide somatostatin analog treatment suppresses paraneoplastic GHRH secretion by the tumor as well as eutopic pituitary GH hypersecretion resulting in a (near) normalization of pathologically elevated insulin-like growth factor-1 *(39,40)*. Tumor-induced osteomalacia, also called oncogenic osteomalacia, is

presumably caused by the paraneoplastic production of phosphatonins, which cause renal phosphate wasting. Because these tumors may express SSTR2, this syndrome may well respond to octapeptide somatostatin analog therapy *(41,42)*. Only infrequently, neuroendocrine tumors that also express SSTR2 may produce parathyroid hormone–related peptide, which is the main cause of humoral hypercalcemia of malignancy. In these selected cases, a trial with an octapeptide somatostatin analog may improve the clinical and biochemical pictures *(43–45)*.

The second stage of the therapeutic work-up of a patient with an endocrine tumor of the GI tract is control of tumor growth. Meticulous localization is mandatory for the patient's work-up for therapy. Knowledge of the natural history of the tumor is very essential. Less than 10% of insulinomas show malignant behavior, whereas 60–90% of gastrinomas and 40–70% of VIPomas are malignant *(12,46)*. Well-differentiated endocrine tumors of the GI tract are generally slow growing; in the case of metastatic disease, long periods of stable disease with relatively good quality of life can be observed *(47)*, and even spontaneous tumor regression has been anecdotally reported *(48–51)*.

On the basis of in vitro studies demonstrating antiproliferative and apoptotic effects of octapeptide somatostatin analogs *(52)*, uncontrolled prospective studies using standard doses of sc octreotide, Sandostatin LAR, or Lanreotide SR have been designed in patients with progressive endocrine tumors of the GI tract. However, only limited numbers of patients have been studied. Anaplastic tumors have been excluded from most studies. Stable disease lasting for a minimum of 3 mo and a maximum of 5 yr was attained in 20–70% of patients and only a partial response in <6% of patients *(53–60)*. Preliminary studies have shown that ultrahigh doses of the currently available octapeptide somatostatin analogs may cause tumor shrinkage in selected patients *(61,62)*. Synergistic effects with combination therapy of octapeptide somatostatin analogs with interferon-α have been reported, and prospective trials have been designed to confirm these results *(63–68)*.

Somatostatin receptor–mediated endocytosis is of particular importance when radiotherapy or chemotherapy of SSTR2 and SSTR5-positive metastatic carcinoids and pancreatic neuroendocrine tumors with α- or β-emitting isotopes or chemotherapeuticals coupled to somatostatin analogs are considered *(69)*. The process of internalization might bring the radioligand or cytotoxic somatostatin analog closer to the nucleus and its DNA *(70)*. A high uptake of radioactivity or the chemotherapeutical is necessary, because nonneoplastic tissues expressing ssts should not be exposed to the toxic effects of the radioligand or cytotoxic analog. ^{111}In-pentetreotide ([^{111}In-DTPA^{0}, D-Phe^{1}]octreotide) emits both Auger electrons (which have a tissue penetration of only 0.02–10 μm) and conversion electrons, with a tissue penetration of 200–500 μ. High doses of ^{111}In-pentetreotide inhibited growth of SSTR2-positive tumor cells in vitro *(71)*. It has also been shown that ^{111}In-pentetreotide can inhibit the growth of liver metastases after injection of SSTR2-positive tumor cells into the portal vein of rats *(71)*. In patients with metastatic neuroendocrine tumors, therapy with ^{111}In-pentetreotide resulted in partial responses in 31–67% of patients, 0–31% of patients had stable disease, and progressive disease was observed in 33–38% *(72–78)*. Therapy with somatostatin analogs coupled to β-emitting radionuclides, such as ^{90}Y and ^{177}Lu, is potentially more effective, because higher tumor radiation doses can be achieved and the longer range of the β-particles (1–10 mm) may also lead to irradiation of neighboring receptor-negative tumor cells (so-called cross fire).

Therapy of patients with endocrine tumors of the digestive tract with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide, (^{90}Y-DOTATOC or ^{90}Y-SMT487/OctreoTher®) resulted in partial responses in 7–22%, stable disease in 49–83%, and progressive disease in 10–32% *(79–84)*. Therapy with [^{177}Lu-DOTA^{0},Tyr^{3}] octreotate in 33 patients with endocrine tumors of the GI tract showed partial remission in 11 patients (33%), minor responses in 2 patients (6%), 13 patients with stable disease (39%), and 7 patients with progressive disease (21%) *(85)*. Major toxicities observed in trials with tumor-targeted radiotherapy were the development of myelodysplastic syndrome and/or acute myeloid leukemia in three patients in a phase I study with ^{111}In-pentetreotide *(78)* and delayed renal insufficiency in a study with ^{90}Y-DOTATOC *(86)*. In the other trials, hematologic side effects were generally mild and transient, and there was no major hepatic or renal toxicity, but there was evidence for gonadal toxicity in humans with ^{111}In-pentetreotide *(78)*. It is evident that only those patients with a high uptake in the tumor deposits as, e.g., shown by ^{111}In-pentetreotide scintigraphy are good candidates for these therapies and that patients with scan-negative tumor deposits will not benefit.

Octapeptide somatostatin analogs have also been coupled to various cytotoxic compounds *(87–94)*. Using the currently available analogs, somatostatin receptor–targeted chemotherapy may also prove to be only effective in SSTR2- and SSTR5-positive tumors *(83,95,96)*.

Applications of Somatostatin Analogs in Other GI Disorders

Prospective randomized studies have demonstrated the effectiveness of octapeptide somatostatin analogs in the management of chemotherapy-related (especially 5-fluorouracil and cisplatin-induced) and acquired immunodeficiency syndrome–related diarrhea *(97–110)* and in reducing postoperative complications of pancreatic surgery. These drugs have been used to decrease the output of enterocutaneous pancreatic fistulas and are prophylactically used to prevent the development of these fistula *(110,111)*. The American Gastroenterological Association has adopted octreotide acetate as initial therapy for the management of acute variceal

bleeding in cirrhotic patients *(111,112)*. Octreotide is currently being evaluated in randomized studies for the treatment of advanced hepatocellular carcinoma *(113)* and malignant intestinal obstruction *(114)*.

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