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REVIEW

The Zollinger-Ellison syndrome: is there a role for somatostatin analogues in the treatment of the gastrinoma?

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Abstract
Purpose Analyze the role of somatostatin analogues (SSAs) in the treatment of sporadic and MEN1-related gastrinomas, trying to define whether recent trials have changed the landscape of gastrinoma therapy.
Methods We evaluate the rationale of SSA use in the treatment of gastrinomas, summarize the current literature concerning the effect of SSAs on the control of Zollinger-Ellison syndrome (ZES) and gastrinomas tumor progression and discuss their role in the most recent guidelines.
Results The medical treatment of gastrinoma and related ZES is aimed at controlling acid hypersecretion and tumor progression, in inoperable patients. The use of proton pump inhibitors (PPIs) to control the syndrome is a cornerstone in the ZES therapy. SSAs are not usually indicated for anti-secretory purpose, because PPIs are considered the treatment of choice, due to their long lasting high efficacy and oral availability. The antiproliferative effect of SSAs has been established by two placebo-controlled trials that have clearly demonstrated a significant increase in progression free survival in patients affected by non-functioning well-differentiated advanced neuroendocrine tumors (NETs). The recent ENETS guidelines recommend the use of SSAs in advanced well differentiated NETs as antiproliferative agents.
Conclusions The high sstr-expression in gastrinomas make them highly responsive to SSAs and support the use of such drugs to counteract the tumour growth in patients not amenable to surgical cure. Unfortunately, limited data, mainly case reports or small series, support the use of SSAs in advanced gastrinomas, therefore, it is difficult to quantify their ability to control tumour growth and disease progression.

Keywords Somatostatin · Somatostatin analogues · Neuroendocrine tumours · Gastrinoma

Introduction

Zollinger-Ellison syndrome (ZES) was firstly described 62 years ago (in 1955), when two patients with severe, recurrent, multifocal ulcerative lesions of the proximal gastrointestinal tract, refractory to any attempt at surgical resection were reported [1, 2]. Subsequently, it was observed that some cases of ZES were sporadic, whereas others occurred in the context of a genetic syndrome known as Multiple Endocrine Neoplasia type 1 (MEN1) [3].

Currently, the natural history of gastrinoma and ZES is well established. However, some controversies about the management of these tumours still exist and the role of somatostatin analogues (SSAs) in their treatment, notably in the advanced gastrinomas, needs to be further debated.

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Zollinger-Ellison syndrome

Epidemiology

ZES has an incidence of 1–1.5 cases/million/year caused by gastrin hypersecretion from duodenal or pancreatic neuroendocrine tumours (pNETs) [4]. Pancreatic gastrinomas represent about 15% of all pNETs and are the second most frequently occurring functional pNETs. The sporadic form is usually diagnosed between the ages of 50 and 70 years with a male to female ratio of 1.5–2:1 [5]. In about 20–30% of patients, ZES is part of a MEN1 syndrome [6].

Clinical presentation and diagnosis

Since the first description of ZES in 1955, the clinical presentation of patients affected by gastrinomas has radically changed [1]. The classical syndrome due to uncontrolled acid hypersecretion and characterized by severe and complicated peptic ulcer disease i.e., vomiting, diarrhoea, heartburn, bleeding, and weight loss, is often masked by the chronic administration of proton pump inhibitors (PPIs) [7]. Consequently, ZES patients often present with less severe ulcer or gastroesophageal reflux disease. Moreover, the disappearance of diarrhoea during treatment with PPIs is a hallmark in these patients and it should raise the suspicion of ZES.

In about one fourth of cases, gastrinomas are associated to MEN1, an autosomal dominant syndrome due to a germline mutation of the *MEN1* gene, located on chromosome 11q13. It is classically characterized by the presence of parathyroid, pancreatic-duodenal and pituitary tumours [8]. Sometimes, ZES can be the first manifestation of MEN1, even though primary hyperparathyroidism is classically the presenting feature in the majority of cases [9–11]. Chronic hypergastrinemia in ZES/MEN1 can stimulate proliferation of gastric enterochromaffin-like (ECL) cells leading to type 2 gastric neuroendocrine tumors (NET) development.

More than 40% of duodenal and pancreatic gastrinomas, MEN1-related or not, show lymph node metastases at diagnosis with no effect on the overall survival. Up to 60% of pancreatic gastrinomas develop liver metastases, while they are less frequent (10–20%) in duodenal gastrinomas, and generally occur late in the course of the disease [9, 12–15]. Finally in 6% of patients with gastrinoma, Cushing's syndrome, due to ectopic ACTH secretion, can complicate the clinical course leading to a poorer prognosis [4]. Generally, the diagnostic delay in ZES is about 5 years and can have a negative impact on the clinical course and prognosis.

The biochemical diagnosis of ZES is based on the demonstration of hypergastrinemia associated with basal gastric acid hypersecretion. A serum gastrin value greater than ten times the upper normal limit (>1000 pg/mL) in presence of gastric acid (i.e., a gastric pH less than 2) is diagnostic for ZES [7]. When the basal gastrin levels are not diagnostic for ZES, a secretin test should be performed [2]. An increase in gastrin levels greater than 120 pg/mL over basal fasting levels is considered positive with a sensitivity and a specificity of 94 and 100%, respectively [16]. Gastrin levels should be measured after withdrawal of PPI treatment for at least 5–7 days considering that the hypoclorydria induced by PPIs is one of the most frequent causes of hypergastrinemia. However, in patients with ZES the PPI discontinuation can cause a dangerous abrupt rebound of acid secretion, thus some authors recommend performing diagnostic evaluation under PPI protection [17].

Upper endoscopy, contrast-enhanced abdomen computer tomography (CT), or magnetic resonance imaging and ^{68}Ga PET/CT [18, 19] can be used to localize the tumour. Endoscopic ultrasound has higher sensitivity in detecting small pancreatic tumours and permits fine-needle aspiration for histological identification [18]. Finally, because approximately 20% of gastrinomas occur in the context of MEN1 syndrome, careful evaluation for genetic screening is indicated [8].

Surgical treatment

Before the introduction of H2-receptor antagonists [20] and PPIs [21], surgery was primarily aimed at the control of gastric acid hypersecretion symptoms and prevention of its sequelae, mainly through a total gastrectomy, vagotomy or, when possible, tumour resection [22, 23]. The ability of medical therapy to effectively manage this syndrome has shifted the role of surgery on the oncological disease itself and therefore onto its ability to identify and resect the tumour and eventually its metastases [23–30].

In sporadic forms, a surgical approach with curative intent is at present mandatory, unless there are contraindications; the standard surgical procedure is represented by exploration through laparotomy for pancreas gastrinomas and duodenotomy for duodenal gastrinomas [31] and finally the dissection of the regional lymph nodes. Pancreatic head tumours should be preferentially enucleated, while body or tail lesions require intermediate or distal pancreasectomy. Whipple procedure (DCP) should be reserved for selected cases [32].

Despite high postoperative cure rates [33, 34], both the biochemical and morphological recurrences are frequent during the follow-up [35, 36].

The survival improvement due to surgery has only been recently demonstrated because these tumours generally progress very slowly and a long-time follow up is required [37].

In the sporadic forms, surgery with curative intent is suggested not only for patients with positive preoperative imaging, but also for patients without preoperative tumour localization at imaging [38], while the surgical cure-rate for patients with MEN1-ZES is virtually nil [33] and surgical management of these patients still remains controversial [39]. Liver metastases represent the main prognostic factor of survival and for this reason, surgery in these patients is generally recommended only to remove pancreatic gastrinomas greater than 2 cm [18, 40].

Medical treatment

Gastrinomas have two important treatment aspects and both must be dealt with, the control of the hormone-excess state, which causes the most debilitating symptoms and the control of tumour growth and prevention of metastatic spread [9, 41, 42].

Control of acid hypersecretion

The antisecretory drugs, such as histamine H_2 antagonists and PPIs are currently recommended to control the acid secretion and symptoms linked to the syndrome [25, 43]. Histamine H_2 receptor antagonists show a good potency to inhibit acid gastric secretion, but poor efficacy in the long term [44–47].

PPIs currently represent the drugs of choice for the treatment of acid hypersecretion in ZES patients, due to their efficacy and long duration [25, 43]. Long-term PPI treatment has not shown to induce tachyphylaxis and it is quite safe [21, 48], even though it can delay the diagnosis and consequently the treatment of the underlying tumour, which is likely to favour disease progression [29, 49, 50].

Long-term PPI-induced hypo-/achlorhydria may induce side effects such as the malabsorption of elements requiring gastric acid secretion, i.e., vitamin B12, iron, and calcium [51–64].

In addition, patients with MEN1-ZES have a high risk of ECL-cell proliferation and gastric carcinoid tumour onset [65, 66], while patients with the sporadic form rarely develop gastric carcinoid tumours [65, 67] and there is no evidence of increased gastric carcinoid tumour incidence in patients with ZES on PPI treatment.

Control of advanced disease

In patients affected by advanced unresectable gastrinomas, the survival is strictly related to the presence of metastases. In patients without liver metastases, the 10-year survival is about 96%, while when liver metastases occur it ranges from 16 to 78%, depending on biologic behaviour of the neoplasm and to the extent of liver involvement [31]. Similarly to other NETs, in patients with malignant gastrinomas not susceptible of surgical cure, systemic treatments [SSAs, target therapy, chemotherapy, or peptide receptor radionuclide therapy (PRRT)] are generally proposed for the control of tumour growth, particularly in progressive disease.

Phase III studies have led to the registration of everolimus [68] and sunitinib [69], for the treatment of progressive pNETs, including gastrinomas.

Indication to chemotherapy is strictly related to the tumour differentiation and grade. In patients with well or moderately differentiated NETs (low or intermediate grade), a streptozotocine combined with 5-fluorouracil and/or doxorubicine regimen or a capecitabine/temozolomide regimen have been used. The first was associated with 20–40% of objective response rate [70], while the second with a partial response rate of 70% [71].

Did PROMID and CLARINET studies change the gastrinoma treatment perspective?

Long-acting SSAs have been used for a long time as a medical symptomatic treatment of well differentiated functioning NETs. Based on the results of preclinical models and clinical studies [72–78], two important phase III randomized trials were performed, PROMID and CLARINET to evaluate the role of SSAs in the control of tumour progression.

The PROMID study investigated the antitumour effect of octreotide LAR 30 mg in patients with metastatic well-differentiated NETs derived from the midgut [79]. It showed the drug's ability to significantly prolong the time to progression (TTP), reaching a median TTP of 14.3 vs. 6 months in patients on octreotide vs. placebo. The antitumour effects, independent of whether the NET was functional or not, were observed most clearly in patients with either a liver metastatic involvement of 10% or less, and/or in patients in whom the primary lesions had been resected. Stable disease after 6 months of treatment was 67 vs. 37.2% in octreotide vs. placebo group. In the PROMID study, both functioning and non-functioning tumours were included, but only of midgut origin. No patients with gastrinomas/ZES/pancreatic or upper duodenal NETs were enrolled. Therefore, this study does not provide any further support to the use of octreotide in gastrinomas, even though the interesting results in terms of tumour stabilization represent the first significant step in the use of SSAs in non functioning NETs.

In the CLARINET study [80], 203 patients with non-functional midgut, hindgut or pancreatic unresectable NETs were randomized to receive lanreotide 120 mg autogel or placebo once every 28 days for 96 weeks. Forty-two

patients in the lanreotide group and 49 patients in the placebo group had a pNET and, among them, two patients in each group had a gastrinoma. Progression-free survival (PFS), the primary endpoint, was longer in the lanreotide vs. placebo group (not reached vs. 18 months, respectively) and estimated 2-year PFS was 65 vs. 33%, respectively. The effect was similar in low and intermediate grade tumours (Ki67 < 10%) and in patients with high- or low-volume hepatic disease. With respect to the pNETs (91 patients), the median PFS time for placebo was 12.1 months (19 events in 29 patients) vs. not reached for lanreotide (13 events in 32 patients). The lanreotide vs. placebo hazard ratio for this group was 0.58. These results suggest the effectiveness of lanreotide in patients with pNETs, even though the number of gastrinomas is too low to say something about the efficacy of lanreotide in these specific patients.

Overall, the CLARINET and the PROMID studies demonstrated a tumour stabilization in 40–80% and a tumour size decrease in less than 15% of patients with NETs. In addition, on the basis of the results of CLARINET and PROMID, the use of long-acting SSAs is currently recommended in all grade 1 and 2 metastatic NET patients irrespective of the primary origin, tumour burden or functional status.

Rationale for therapy with SSAs in gastrinoma: in vitro and in vivo studies of somatostatin receptor expression

Somatostatin and its analogues act through membran receptors coupled to G-protein, the sstr subtypes 1, 2, 3, 4, and 5 [81]. Two isoforms of the sstr2 (sstr2A and sstr2B) can be generated through alternative splicing [82, 83].

The inhibitory effects of somatostatin on neuroendocrine secretion are mediated by the inhibition of adenylate cyclase activity and calcium influx. On the other hand, the regulation of cell proliferation is mediated by the activation of a phosphotyrosine phosphatase or MAP kinase activity by somatostatin [84, 85].

The majority of sstr-positive tumours simultaneously express multiple sstr subtypes, although there is a considerable variation in sstr subtype expression between the different tumour types and also among tumours of the same type [86–89].

All receptor subtypes bind somatostatin with high affinity, while the SSAs, octreotide and lanreotide, bind the sstr2A with high affinity and the sstr5 and 3 with moderate and a low affinity, respectively.

Although the endocrine digestive tract and endocrine pancreas express all sstrs, the expression of sstr2 seems to be the most prevalent [90]. With respect to ZES, Kulaksiz et al. found that sstr2 was expressed in 100% of gastrinomas, in 58% of insulinomas and 86% of other tumours, while sstr3 and sstr5 were expressed in 79 and 76% of gastrinomas, respectively [91]. In addition, a high and positive correlation was observed between uptake at the somatostatin receptor scintigraphy (SRS) and sstr2A immunohistochemical expression [91]. Octreotide has been reported to suppress gastrin secretion and normalize gastric acid secretion in 50–100% of patients with ZES, reducing the rate of peptic ulceration and diarrhoea [92]. The diffuse expression of sstr2A in gastrin-secreting tumour cells supports the clinical and biochemical control obtained by using SSAs in patients with ZES [93]. Radiolabelled SSAs targeting sstrs have been available for many years. The first commercially available agent was the Indium-111-diethylenetriaminepentaacetic acid-octreotide, originally designed for SRS.

Several studies evaluated the diagnostic performance of SRS in patients affected by ZES [94, 95]. SRS with [^{111}In-DTPA-DPhe1] octreotide was reported to be the most sensitive method either for primary tumour or metastatic liver lesions in 80 patients with ZES. It was considered for more than 15 years the imaging method of choice in patients with ZES for preoperative primary tumour localization, detection of bone or liver metastases [96, 97]. Recently, new SPECT and PET tracers, ^{99m}Tc and ^{68}Ga, were evaluated. Reubi et al. [98] reported the affinity of ^{68}Ga-DOTATATE in binding sstr2 to be approximately ten-fold higher than that of octreotide. ^{68}Ga-DOTATATE-PET has higher diagnostic sensitivity than Octreoscan. ^{68}Ga-DOTANOC appears to have higher diagnostic sensitivity than ^{68}Ga-DOTATATE because its sstr affinity profile includes sstr2, −3, and −5 [99]. Recently the ^{68}Ga-DOTANOC radiotracer has been evaluated in 25 patients with clinical/biochemical diagnosis of ZES with negative or equivocal CT findings, showing a detection rate of 68%, much higher than contrast enhanced CT [100].

All these findings support the peculiar expression and activity of the somatostatin pathway in gastrinomas and candidate these tumours to be highly responsive to SSA treatment. Furthermore, the high density of sstr2 in gastrinoma and the avidity on functional imaging modalities (Octreoscan, ^{68}Ga-PET) suggest that the PRRT may be an optional treatment in patients affected by ZES secondary to malignant gastrinoma [101]. In a study conducted on 129 metastatic NET patients, eight of them with gastrinomas, treated with ^{177} Lu-octreotate a partial remission was observed in 63% of the patients, 25% showed a minor response, only one patient presented stable disease [102]. Recently, Grozinsky-Glasberg et al. reported an improvement of symptoms and a reduction of gastrin secretion in 11 patients with metastatic gastrinomas, treated with PRRT (90 Yttrium or 177LU-DOTATOC). Nine patients were also treated with SSA, with complete tumour response in 9%, a

Table 1 Zollinger-Ellison medical management in recent international guidelines

Guideline	ENETS 2011[a]	ENETS 2016[b]	NCCN 2-2016[c]	NANETS 2013[d]	ESMO 2012[e]
Medical treatment for ZES in non-metastatic pNETs and d-NETs	-Appropriate specific therapy for hormonal excess that is control of gastric acid hypersecretion by H2 blockers or PPIs, acutely and long term. -Long-acting SSA not recommended for acid secretion control	-PPIs are drugs of choice; for patients surgically cured it may be necessary to continue antisecretory drugs at lower doses	-Manage gastric acid hypersecretion with PPIs	- PPIs recommend -NANETS 2010: SSAs are effective in reducing both gastrin and acid secretion however they are rarely used because excellent oral medications are available -2013: consider Octreotide LAR for control of syndrome	-PPIs indicated for symptom treatment -SSA indicated for all functional p-NET
Medical treatment for ZES in advanced metastatic disease	-PPIs in general remain effective in controlling the syndrome also with extensive disease	-PPIs for syndrome control -SSAs not mentioned as effective drugs for syndrome control in metastatic gastrinoma	-Control gastric acid hypersecretion with PPIs	-PPIs recommend	
(d-NETs or p-NETs)	Not specific for gastrinoma: -Long-acting SSAs (G1) -chemiotherapy (G3) -Everolimus and Sunitinib (p-NET)	Not specific for gastrinoma: -Long-acting SSAs (G1 or low G2): first line -Chemiotherapy (G3 or G2 with high tumor burden and/or progressive disease): first line -Everolimus and Sunitinib (p-NET): second line	Not specific for gastrinoma: -Consider octreotide or lanreotide for locoregional resectable and unresectable disease and for metastatic disease -Everolimus and Sunitinib (p-NET) -Cytotoxic chemotherapy	Progressive p-NET (not specific for gastrinoma): -consider octreotide LAR -Sunitinib and Everolimus recommend -Consider chemotherapy	p-NET (not specific for gastrinoma): -SSA indicated for all functional p-NET -Everolimus and Sunitinib (G1/G2) -Chemotherapy (G2/G3)

[a] Fave et al. [104]; Jensen et al. [105]; Pavel et al. [106]

[b] Fave et al. [107]; Falconi et al. [18]; Pavel et al. [108]

[c] NCCN Guidelines Version 2.2016

[d] Kulke et al. [109]; Kunz et al. [110]

[e] Öberg et al. [111]

partial response in 45% and disease stabilization in 45% of patients [103]. These data may suggest that the combination of the two therapies can exert antiproliferative and antisecretory effects in patients with metastatic gastrinoma.

Zollinger-Ellison management in recent international guidelines

We analyzed recent international guidelines (ENETs 2011 and 2016, NCCN 2-2016, NANETS 2013, ESMO 2012) looking for specific indications for ZES medical management. As reported in Table 1, SSAs are not generally suggested for the controlling of this clinical syndrome, considering the durable effectiveness as well as cost-effectiveness of PPIs. In the above-mentioned guidelines [104–111], SSAs are indicated for low grade metastatic gastrinomas, stable or progressive but with low tumour burden, similarly as indicated in other duodenal and p-NETs. In other words, no specific indication for SSA therapy in ZES NETs is reported.

SSA treatment of Zollinger-Ellison syndrome: clinical studies

Reports concerning the ability of SSAs in controlling gastrin levels and symptoms in ZES patients can be found in literature since the development and marketing of these drugs. In many series, patients with ZES were included in a larger group of gastroenteropancreatic NET (GEP-NETs) and, in the majority of them, ZES patients represented a small subgroup. Only in few series, the study population was homogeneous and focused on gastrinoma patients.

Since 1985, some case reports or small series highlighted the effectiveness of SSAs in ZES patients. Wormann et al. successfully treated a patient with ZES and active bleeding from a jejuneal ulcer with continuous infusion for 24 h and then sc injections (100 µg twice daily) of octreotide over a period of 8 months [112]. Subsequently, Ruszniewski et al. treated five patients affected by ZES (3 MEN1) with octreotide (200 µg sc twice daily), showing an improvement of basal acid secretion (BAO) and 87% reduction of gastrin levels, throughout the 12-months follow-up, without tumor regression. Only one patient escaped from SSA treatment after 9 months [113]. Another patient with combined paraneoplastic Cushing's syndrome and ZES was successfully treated by octreotide (initially 200 µg sc twice daily and then 50 µg sc twice daily), withour tumour regression [114].

In a series of nine ZES patients treated with octreotide (100 µg sc three times daily), after 1 year of treatment, the mean gastrin suppression rate was more than 80% in comparison with basal levels in seven patients. During the 2nd year of treatment these results were maintained in four patients and only in one patient gastrin levels were controlled for 42 months. Octreotide was also effective in controlling symptoms with complete response in seven patients (78%) and partial response in the remaining 2 (22%) [93].

In 1992, Arnold et al. reported the interim results of the prospective multicenter phase II trial of the German Sandostatin Study Group, concerning the effect of octreotide (200 µg sc three times a day) on tumour growth in 85 out of 115 enrolled patients affected by malignant NETs, including 12 with gastrinomas. A beneficial effect of octreotide on tumour progression was initially documented, but resulted attenuated by the 12 months follow-up [115]. The same conclusions were achieved on a series of 21 GEP-NETs, of which six gastrinomas, with a more prolonged follow up (up to 59 months, median 15 months) [116]. The final results of the German study in 103 patients were published in 1996. The trial was intended to last 12 months but, in responder patients, the treatment (octreotide 200 µg sc thrice daily) was maintained until progression and the dose was increased (500 µg sc thrice daily) for at least 6 months in 28 patients with documented progression. Eleven out of 103 patients had gastrinomas and eight of which had a documented tumour progression before enrolment. Response to treatment (stable disease) occurred in three out of these patients (37.5%), but the length of the response in this subgroup of patients was not specified [75]. Angeletti et al. treated with octreotide (500 µg sc once a day) ten patients affected by progressive metastatic GEP-NETs of whom four had ZES (two MEN1-associated). The authors reported stable disease in six patients, partial response in one patient affected by gastrinoma and progressive disease in two patients. Biochemical response was documented in 53–78% of the seven evaluable patients at the end of follow-up [117].

In 1999, Gaztambine and Vazquez reported the ability of lanreotide SR (30 mg every 10–15 days) to reduce gastrin levels and control symptoms in two patients with metastatic gastrinomas over a period of 7 months [118].

A prospective open phase II, multicenter study evaluated the effects of lanreotide PR (30 mg in every 14 days over a period of 6 months) on hormone related symptoms, tumour markers, and size and tolerability in a group of 55 patients with progressive GEP-NET (six gastrinomas). Efficacy assessment in the ZES patient subgroup was performed by evaluation of basic acid output and gastrin levels besides the modification in tumour size. Four patients achieved partial response (≥50 decrease) in serum gastrin levels, while in two patients no change had occurred at the end of the study. Tumour size remained stable in three patients, while progression was documented in one [119]. Tomassetti et al.

Table 2 Somatostatin analogue treatment of zollinger-ellison syndrome: clinical studies

Paper	Study design	Total net patients	Gastrinoma/ Men 1	Analogue and doses	Treatment duration	End points
Wormann et al. [112]	Case report	1	1/NR	Octreotide 25 µg/h ev infusion for 24 h, then 100 µg sc twice daily	8 months	Control of bleeding Gastrin levels
Ruszniewski et al. [113]	Prospective study	5	5/3	Octreotide 200 µg sc twice daily	9–12 months	Gastrin levels, antiH2 requirements Tumor growth control, safety
Ruszniewski et al. [114]	Case report	1	1/NR	Octreotide 200 µg sc twice daily initially, then 50 µg sc twice daily	9 months	Cushing syndrome control Gastrin levels Tumor growth control
Mozell et al. [93]	Prospective study	9	9/NR	Octreotide 100 µg sc thrice daily	1–48 months	Gastrin levels Symptom control
Arnold et al. [115]	Prospective multicenter phase II trial	115 (interim report of 85)	12/NR	Octreotide 200 µg sc thrice daily	3–12 months	Tumor growth control
Arnold et al. [116]	Prospective study	21	6/NR	Octreotide 200 µg sc thrice daily	3–59 months	Tumor growth control
Arnold et al. [75]	Prospective multicenter phase II trial	103	11/NR	Octreotide 200 µg sc thrice daily Increase to 500 µg thrice daily (28 pts)	12 months-until progression	Hormonal response Tumor growth control Safety
Gaztambine and Vasquez [118]	Case report	2	2/1	Lanreotide SR 30 mg im every 10–15 days	7 months	Hormonal response Symptom control Safety
Wymenga et al. [119]	Prospective open, phase II, multicenter study	55	6/NR	Lanreotide SR 30 mg im every 7–14 days	6 months	Symptom control Tumor marker variation Tumor growth control QoL
Angeletti et al. [117]	Prospective Study	10	4/2	Octreotide 500 µg sc once a day	12 months	Tumor marker variation Tumor growth control
Tomassetti et al. [120]	Prospective study	16	2/2	Octreotide LAR 20 mg im/28 days	6–15 months	Tumor marker variation Tumor growth control Safety
Aparicio et al. [77]	Prospective study	35	2/NR	Octreotide 100 µg sc thrice daily Lanreotide 30 mg im/ 14 days	1–48 months	Tumor marker variation Tumor growth control Safety

Table 2 continued

Paper	Study design	Total net patients	Gastrinoma/ Men 1	Analogue and doses	Treatment duration	End points
Shojamanesh et al. [121]	Prospective study	15	15/3	Octreotide 200 µg sc twice a day, since 1999 Octreotide LAR 20–30 mg im/28 days	3–54 months	Tumor growth control Effect on survival Gastrin levels Safety
Saijo et al. [122]	Case report	1	1/NR	Octreotide 200 µg sc daily, then 200 µg sc twice a week	32 months	Gastrin levels Tumor growth control
Granberg et al. [123]	Case report	1	1/NR	Octreotide LAR 20 mg im/28 days	3 years	Markers levels Tumor growth control
Yamaguchi et al. [124]	Case report	1	1/1	Octreotide 50 µg sc twice daily, then Octreotide LAR 20 mg im/28 days	>7 years	Symptom control Gastrin levels Tumor growth control

NR not reported

treated with octreotide LAR a group of 16 GEP-NET patients (20 mg in every 28 days for a mean of 10.7 months, range 6–15 months). Two patients were affected by MEN1-ZES, surgically untreated, without liver metastases, clinically controlled by omeprazole and not previously treated with SSAs. Major biochemical response (gastrin level reduction ≥50%) was observed in these two patients and tumour size remained stable [120]. Antitumour efficacy of SSA treatment (octreotide 100 µg sc thrice a day or lanreotide PR 30 mg in every 14 days) was studied in 35 consecutive patients with progressive NETs (slow or rapid progression) [77]. Two patients were probably affected by pancreatic gastrinoma, but nothing is reported about their outcome.

The largest prospective series of malignant gastrinomas treated with SSAs have been published in 2002 on 15 consecutive patients, three with MEN1. All patients had liver metastases and rapid or slow progression over 3–6 months before starting the treatment with octreotide (initially 200 µg sc twice a day, since 1999 LAR formulation 20–30 mg in monthly). Treatment was continued until severe side effect development (two patients with paraneoplastic Cushing's syndrome), complete disease remission or significant progression (development of new lesions or bone metastases, >25% increase of pre-existing lesion). After 3 months, 53% of patients had a tumour response (stabilization in seven and partial response in one patient). Seven out of fifteen patients (47%) were considered non-responders. All responders had slow tumour growth before octreotide treatment. However, two of these patients subsequently developed tumour progression. Six out of fifteen patients (five responders and one non responder) presented a statistically not significant decrease in serum gastrin levels after 3 months of treatment compared with pre-treatment. In responders, the response was generally long-lasting (mean 25 ± 6 months, range 5.5–54.1 months) [121].

Saijo et al. [122] reported a case of malignant duodenal gastrinoma, for which octreotide treatment (initially 200 µg sc daily and then at a minimal dose of 200 µg twice a week) was able to stabilize progressive liver metastases and control serum gastrin levels, which had been unresponsive to dimethyltrizenoimidazole carboxamide treatment [122]. Another impressive case of a pancreatic gastrinoma, metastatic to the liver, which had almost complete radiological and biochemical response to octreotide LAR (20 mg in every 4 weeks), was reported by Granberg et al. [123].

Finally, Yamaguchi et al. [124] reported the case of a young woman with multiple duodenal gastrinomas associated with MEN1 and metastatic to the liver, with long-lasting (more than 7 years) biochemical response to octreotide (initially 50 µg sc twice a day and then LAR formulation 20 mg in once a month). During the prolonged follow up a very slow tumour growth was documented

[124]. The above-mentioned studies are summarized in Table 2.

Discussion

Clinical manifestations and morbidity of gastrinomas and ZES have been dramatically changed since the availability of histamine H_2 antagonists and PPIs. In the past ZES patients died for severe peptic ulcer disease due to uncontrolled gastric hyperacidity and surgery represented the only treatment for these patients aimed to the control of the gastric acid hypersecretion. The use of PPIs has allowed the stable control of the clinical syndrome, blocking the final action of inappropriate gastrin secretion on acid-producing cells of the stomach, with a prolonged effect over time, in the absence of escape. On the other hand, the undoubted PPI efficacy has produced mild clinical pictures of the syndrome leading to diagnostic delays of which prognostic consequences are not entirely irrelevant. Indeed, in ZES, gastrin hypersecretion is due to a NET, sometimes multiple, localized in the pancreatic-duodenal area, rarely aggressive, slow growing, but still with potential malignant behaviour. In these patients the prognosis is strongly influenced by liver metastases occurrence and the late diagnosis favours the appearance of metastatic spread, more frequently to the lymph nodes, but also to the liver. Furthermore, in patients with localized disease, despite high surgical cure rates the recurrences are frequent during the follow-up. Thus, in patients affected by gastrinoma and ZES we cannot be satisfied by the only achievement of adequate gastric acid hypersecretion control, preventing its sequelae, even though this should be considered a great target. In addition, we must aim towards the medical treatment of the neoplastic disease itself, when surgery has failed or is no more indicated. Although SSAs have been used for long time as symptomatic treatment for functioning NETs, some preclinical and clinical investigations have also reported a tumoristatic effect on well differentiated NETs. The PROMID and CLARINET studies showed that SSAs are able to slow down tumour progression in 40–80% of NETs. On the basis of these studies, the long-acting SSAs are currently recommended in the treatment of patients with grade 1 and 2 metastatic NETs, irrespective of primary origin or functional status.

The high sstr expression in gastrinomas make them highly responsive to SSA treatment and support the use of such drugs to counteract the tumour growth in gastrinoma patients, not amenable to surgical cure. One more argument in favour of treatment with SSAs in MEN1-ZES is the frequent association of multiple duodenal gastrinomas with not functioning pNETs, that still represent the syndromic manifestation conditioning the survival of MEN1 patients. Moreover, PPI therapy is not targeted to the reduction of gastrin secretion and consequently it is not able to counteract the gastrin trophic effect on ECL-gastric cells, with the possible onset of gastric carcinoids, although they occur in particular cases (MEN1-ZES).

As summarized, a number of reports have appeared in literature in the past 30 years, concerning the ability of SSAs in controlling gastrin levels, symptoms and in stabilizing tumour growth in ZES patients. The SSA treatment has been shown to be able to control gastrin levels and ZES symptoms in most patients reported. Nevertheless, it is difficult to quantify their ability to control tumour growth and disease progression, because the above reported case series were heterogeneous, with low patient numbers, using different SSA formulations (intermediate acting SSAs and SSA depot formulations). Finally, the criteria to define response or progression of the disease were not comparable. Overall SSA treatment appeared to stabilize slow progressive malignant gastrinomas, even for a prolonged period. In addition to these considerations, the safety profile of these drugs even in long-term treatments must be emphasized. Therefore even if effective and inexpensive drugs are available for symptomatic control of ZES syndrome, currently we cannot abdicate a therapeutic attempt to treat the underlying tumour disease.

In the end, more prospective studies need to be performed to better clarify the efficacy of SSAs in gastrinoma tumor growth stabilization.

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Compliance with ethical standards

Conflict of interests A.C and A.F report support to research from Novartis, Ipsen and Italfarmaco. The remaining authors declare that they have no competing interests.

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