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REVIEW

Escalated-dose somatostatin analogues for antiproliferative effect in GEPNETS: a systematic review

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Abstract

Background/Purpose Somatostatin analogues are the cornerstone of systemic therapy for metastatic well-differentiated gastroenteropancreatic neuroendocrine tumours for both hormonal control and antiproliferative effect. Dose escalation of somatostatin analogues is often utilized in clinical practice, but small studies have yielded mixed results. The aim of this study was to systematically determine the efficacy and safety of escalated-dose somatostatin analogues in the above setting.

Methods Eligible trials (using more than 30 mg octreotide or 120 mg lanreotide/28 days) were identified from MEDLINE, EMBASE, other databases and conference proceedings. Demographics, disease control rate, objective response rate, biochemical response, improvement in symptoms and toxicity were abstracted. Trials were synthesized qualitatively.

Results Eighteen studies (1002 patients) were identified. The risk of bias was moderate for objective response outcomes, but high for the outcomes of symptom control and toxicity due to open-label trial designs. Disease control rates ranged from 30 to 100%, but response rates were modest (at 0–14%). Rates of biochemical improvement (27–100%) and symptom improvement (23–100%) ranged widely depending on the population studied and the definition of response. The most common toxicities were fatigue, diarrhoea, abdominal discomfort and cholelithiasis, with no severe or unexpected toxicities compared to standard-dose somatostatin analogues.

Conclusions The current evidence indicates that escalated-dose somatostatin analogues are well-tolerated in patients with gastroenteropancreatic neuroendocrine tumours, with significant rates of disease control but low rates of tumour response. It was difficult to judge the exact rate of biochemical response or symptomatic improvement. There is a need for large, prospective studies investigating the role of escalated-dose somatostatin analogues in the treatment of metastatic gastroenteropancreatic neuroendocrine tumours.

Keywords SSA · Somatostatin · Octreotide · Lanreotide · Neuroendocrine tumour · Systematic review

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Background

Neuroendocrine tumours (NETs) arise from enterochromaffin cells and can present throughout the body, but most commonly occur in the gastrointestinal tract and lung. They display marked heterogeneity in biologic characteristics, clinical behaviour and prognosis. Histological grading (along with site of origin) is commonly used to separate NETs into subgroups with comparable aggressiveness for optimal selection of treatment and study of new therapies in

clinical trials [1]. Multiple options for systemic treatments exist for Grade 1–2 NETs, including somatostatin analogues (SSAs), everolimus, sunitinib (for pancreatic NET) and peptide receptor radionuclide therapy (PRRT) (for midgut NET), with robust evidence for each from randomized controlled trials [2–7]. SSAs evolved from use for management of secretory (carcinoid) symptoms to be proven as an antiproliferative agent. Hence they are generally considered as the first-line treatment of choice for both secretory and non-secretory G1−2 NETs due to their efficacy, tolerability and ease of administration [8], although different options exist depending on the site of the primary (pancreatic, bronchial, small bowel/unknown or other). They remain the most common treatment for NETs worldwide.

The commercially available long-acting SSAs (octreotide, lanreotide) bind the somatostatin receptor subtypes that are overexpressed on ~60–80% of well-differentiated NETs [9, 10]. They inhibit release of various pro-growth factors, such as GH, glucagon and insulin, to improve carcinoid symptoms of flushing and diarrhoea [11], with corresponding decreases in levels of the biomarkers chromogranin A (CgA) and urinary 5-hydroxyindolacetic acid (5-HIAA). In addition, SSAs exert negative effects on cell growth by direct inhibitory mechanisms, such as apoptosis or cell cycle arrest. The antiproliferative effect of SSAs has been demonstrated in the PROMID and CLARINET trials, two pivotal phase III trials that demonstrated significant lengthening of time to progression and progression-free survival (PFS) with SSA compared to placebo [2, 12].

Although SSAs are a cornerstone of NET therapy, the optimal dose of SSA for antiproliferative effects is not yet determined. The doses employed in the trials above were similar to those used for control of hormonal hypersecretion, namely, octreotide LAR 30 mg (PROMID) and lanreotide ATG 120 mg (CLARINET) every 28 days. There is no high-quality evidence investigating whether higher dosages may achieve a greater impact on tumour control, although similar studies in acromegaly have demonstrated possible benefit for escalation of lanreotide and octreotide in patients with inadequate control on standard dosages [13, 14]. Given the significant peak-to-trough variation of SSAs [15, 16], dose escalation may prolong the time that SSA concentration is in the desired therapeutic range, thereby improving efficacy. This was first postulated from case reports and small series [17, 18]. In recent years, several retrospective studies [19, 20] and small prospective studies [21, 22] have investigated this issue, but with mixed reports of impact on efficacy and concerns about increased toxicity, particularly cholelithiasis and nausea [23, 24].

We undertook this systematic review to assess the current literature regarding the efficacy and safety of escalated-dose SSA in the symptomatic and antiproliferative treatment of GEPNETs.

Aim

To determine the efficacy and safety of escalated-dose SSA in treatment of metastatic GEPNET.

Methods

Eligibility criteria

Eligible studies investigated the use of either octreotide or lanreotide in patients with histologically confirmed NET. We elected to exclude studies of pasireotide, as no standard dose has been established for clinical practice, and thus it was not possible to define escalation of dose. Both retrospective and prospective studies were included; single-arm studies were also eligible. To be included, a study needed to report on participants treated with octreotide at a dose higher than 30 mg every 28 days or lanreotide at dosages higher than 120 mg every 28 days. For studies investigating short-acting SSA, an average dose of 30 mg of octreotide per 28 days or 120 mg lanreotide per 28 days was considered escalated-dose treatment (given the lack of a standardized dose in trials investigating short-acting SSA). Reviews of SSA were scrutinized for references to eligible trials, but were themselves excluded. Studies of Merkel cell carcinoma, phaeochromocytoma and medullary thyroid carcinoma were also excluded, as were reports with less than five patients or where there was no report on any of the considered endpoints.

Search strategy

We performed a literature search of MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic reviews, ACP Journal Club and DARE on 10 May 2016. A handsearch of the Proceedings of the ASCO, ASCO GI and ENETs conference abstracts from 2013 to 2016 was performed on 11 May 2016. The search strategy is described in supplementary data 1. The protocol was not centrally registered.

The primary endpoint was response rate, defined as a composite of complete and partial response. Secondary endpoints included disease control rate (composite of complete response, partial response and stable disease), biochemical response, PFS, overall survival (OS) and toxicity. Studies were classified according to prospective/retrospective nature and whether patients had received prior SSA.

Study selection and data extraction

The methods of potentially eligible studies were assessed independently by two reviewers (DLC, DF). Studies considered potentially eligible were retrieved in full and

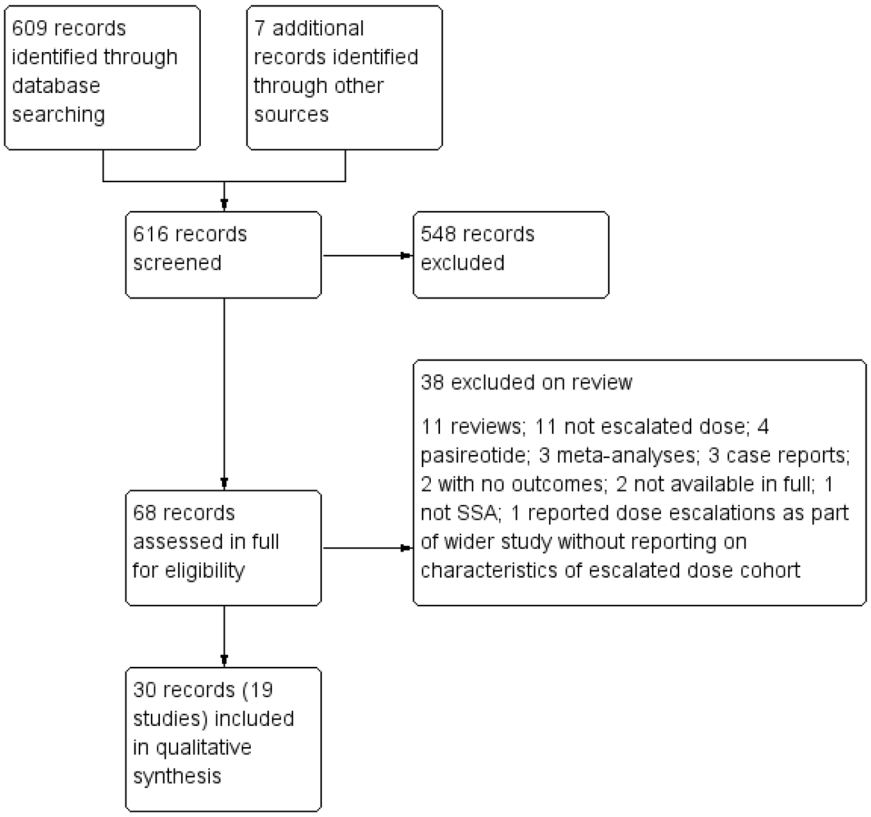

Fig. 1 Study flow diagram.

evaluated. Disagreements were resolved by consensus or referred to a third reviewer for arbitration (SS).

Information extracted from studies included study identifiers, inclusion/exclusion criteria (particularly prior use of SSAs), demographics, details of the interventional and control arms (where present) and length of follow-up. Risk of bias assessments were performed with the ROBINS-I criteria [25] for prospective studies, and the Newcastle-Ottawa Scale for retrospective studies.

We aimed to summarize the defined endpoints qualitatively, without performing meta-analysis, because of the anticipated heterogeneity in trial designs, patient populations (different primaries), indications for dose escalation (symptoms or disease control), type of SSA employed (octreotide, lanreotide, short-acting or long-acting), prior SSA use and measurement of outcomes. For trials that reported the effects of multiple dose escalations on symptom control in the same patient, the effect of the first dose escalation was abstracted where possible to avoid repetition.

Results

Study selection

The results of the search are detailed in the CONSORT diagram (Fig. 1).

Study characteristics

The 18 studies included for analysis, 11 prospective [7, 22, 26–34] and seven retrospective [19, 20, 35–39], comprised a total of 1002 patients (Table 1A and 1B). Two randomized studies were included, which had treatment arms not satisfying the inclusion criteria (PRRT in Strosberg 2017; pasireotide in Wolin 2015); the relevant arms were abstracted and included in data synthesis.

Excluded studies

Although Koumarianou et al. stated in their abstract that octreotide 30 mg was used as part of treatment every 3 weeks, the full publication of this study [40] detailed that while bevacizumab and temozolomide was given every 3 weeks, octreotide was given every 4 weeks, i.e. as standard dose. Woltering 2006 and Markovich 2012 did not report any of the primary or secondary endpoints.

Risk of bias

The included prospective studies were all at moderate risk of bias for the outcomes of response rate, PFS and OS due to their protocol-defined objective determination of these outcomes (Supp. Table 1). They were not assessed at being low risk because of potential bias from confounders.

Table 1A Characteristics of included studies—prospective studies

Prospective trials	Primary/ number	Prior SSA?	Intervention	Reason for dose escalation	Symptoms	DCR	ORR	Biochemical response	Toxicity
Strosberg 2017	Metastatic SBNET (230)	Y	Octreotide LAR 60 mg (115)	Tumour progression	NR	65%	3%	NR	34% any adverse event related to treatment, 1% G3−4
Albertelli 2016	Metastatic NET (35)	Y	Lanreotide ATG 180 mg/4 weeks	Tumour progression	NR	NR	NR	NR	21% any SAE; 3% SAE related to treatment (cholelithiasis/cholecystitis)
Wolin 2015	Metastatic GEPNET (57)	Y	Octreotide LAR 40 mg/28 days ($n = 57$) vs. Pasireotide LAR 60 mg/28 days ($n = 53$)	Carcinoid symptoms	12/45	75%	2%	NR	Hyperglycaemia (5%), fatigue (3%), cholelithiasis (5%), injection site pain, LFT derangement, diarrhoea (2% each)
Ferolla 2012	Metastatic NET (28)	Y	Octreotide LAR 30 mg/21 days	Flushing 25%, diarrhoea 36%, bronchoconstriction 7%, pain 21%, weakness 14%, no symptoms 32%	100%	100%	7%	CgA 30%, u5HIAA 57%, Gastrin 100%	Diarrhoea (4%), abdominal pain (4%), cholelithiasis (8%), pyrexia (4%)
Welin 2004	Midgut NET (12)	Y	Octreotide 160 mg/ 2 weeks for 2 months, then monthly	NR	NR	75%	0%	CgA 33%, u5HIAA 16%	Gallstone (8%), fever (50%)
Faiss 1999	Foregut NET (30)	Y (or prior interferon)	Lanreotide 5 mg tds	Tumour progression	Diarrhoea significantly improved as a group	43%	6%	Decreased (CgA/ u5HIAA)	Fatigue (30%), steatorrhoea (6%), cholelithiasis (3%)
Eriksson 1997	SBNET/PNET (19)	N	Lanreotide 750 mcg qid to 3 mg qid	NR	Flushing better ($p = 0.06$)	NR	NR	58% (u5HIAA/ CgA)	4 ceased due to AE (gallstone, diarrhoea)
Imam 1997	Metastatic NET (8)	N	Lanreotide 12 mg/day	NR	NR	100%	0%	71% (CgA/ u5HIAA)	NR
Arnold 1996	Metastatic GEPNET (52)	Y	Octreotide 500 mcg tid	Tumour progression	NR	37%	0%	NR	NR
Di Bartolomeo 1996	SBNET/PNET (58)	N	Octreotide 500 mcg tid ($N = 23$) or 1000 mcg tid ($N = 35$)	NR	Diarrhoea improved in 40%, flushing in 50%	50%	3%	77% (u5HIAA)	Gallstones (4%), Steatorrhoea (4%)
Anthony 1993	NET (28)	Y	Octreotide 500–2000 mcg tid, Lanreotide 3000 mcg tid	NR	Flushing "significantly reduced" with octreotide, $p < 0.05$ on VAS	42% (6/13 octreotide, 5/13 lanreotide)	31% (4/13 octreotide, 4/13 lanreotide)	NA	Steatorrhoea with octreotide; injection site discomfort, mild abdominal cramping and gallstones (1) with lanreotide

Table 1B Characteristics of included studies—retrospective studies

Retrospective trials	Primary/ number	Prior SSA?	Intervention	Reason for dose escalation	Symptoms	DCR	ORR	Biochemical response	Toxicity
Shen 2016	Metastatic NET (59)	NR	Octreotide > 30 mg/28 days	NR	NR	NR	NR	NR	NR
Faggiano 2015	Metastatic NET (14)	Y	Lanreotide 120 mg/21 days (4), Lanreotide 120 mg/14 days (4), Octreotide LAR 30 mg/21 days (4), Octreotide LAR 30 mg/ 14 days (2)[a]	NR	80% improved (4/5)	85%	14%	NR	NR
Modica 2015	Metastatic NET (21)	Y	Octreotide LAR (15), lanreotide (6)	NR	63% improved	53%	5%	NR	Abdominal discomfort (5%), gallstones (5%), T2DM (5%)
Al efraij 2015	Metastatic NET (37)	Y	Octreotide 40–60 mg/month	Diarrhoea 43%, flushing 30%, progression 27%, increased markers 22%	Diarrhoea 63%, flushing 91%, bronchoconstriction 25%, abdominal pain 53%	30%	0%	CgA 31%, u5HIAA 23%	NR
Strosberg 2014	Metastatic NET (239)	Y	Octreotide 40–133 mg/month	NR	Diarrhoea 79%, flushing 81%	NR	NR	NR	NR
Anthony 2011	Metastatic NET (136)	NR	Octreotide 40–60 mg/month	Lack of efficacy (in 65%)[a]	NR (by dose)	60% (72/120)	7% (8/120)	NR	NR (by dose)
Chadha 2009	Metastatic NET (54)	Y	Octreotide LAR 40–90 mg/ 28 days	Diarrhoea 83%, abdominal pain 33%, flushing 21%, palpitations 6%	NR	NR	NR	NR	NR

[a] 65% of overall population (Octreotide 20-60 mg/month), *tid* thrice a day, *VAS* visual analogue scale, *DCR* disease control rate, *ORR* objective response rate, *CgA* chromogranin A, *u5HIAA* urinary 5-hydroxyindolacetic acid, *SAE* special adverse events, LFT liver function tests, *AE* adverse events, *NR* not reported

However, they were at serious risk of bias for outcomes relating to symptomatic relief and safety profile, mainly because of their open-label nature. The exception was Wolin 2015, which was a double-blinded study and thus was at moderate risk for symptomatic relief and safety profile [26]. Although nurses administering the injections were not blinded to the formulations of octreotide and pasireotide (which differ in physical appearance), they were not involved in outcome assessment and the patient and treating clinicians remained blinded.

The retrospective studies generally had a low risk of bias as measured by the Newcastle-Ottawa scale, with scores ranging from 5 to 7 (Supp. Table 2). The two studies scoring 5 [19, 36] received fewer points for comparability of cohort (as these studies did not analyse outcomes by important factors, such as histological grade) and did not comment on adequacy of follow-up.

Description of included studies

Of the 18 studies included, 11 were prospective and seven were retrospective. Two of these were randomized controlled trials, but both compared escalated-dose SSA to therapy other than standard-dose SSA (PRRT and pasireotide, respectively) [7, 26]. Thus, only the results of the escalated-dose SSA arm were incorporated in qualitative synthesis. Eleven studies investigated octreotide, four involved lanreotide and three reported outcomes from both. The majority of trials allowed patients with metastatic NETs from any origin, but eight restricted enrolment to gastrointestinal primaries. Thirteen required the prior use of standard doses of SSAs whereas three did not; two did not provide this information.

The SSA used and the dosage employed also varied between studies. Doses used for octreotide ranged from 30 mg/21 days [27] to 160 mg/2 weeks [28]; for lanreotide doses ranged from 180 mg/4 weeks [22] to 15 mg/day [29]. All prospective studies treated with SSA without other concurrent antiproliferative treatment; the majority mandated a washout period of 4 weeks prior to commencing therapy. However, information about concurrent anticancer treatments was poorly reported in the retrospective studies.

Disease response rate

Thirteen of the 18 studies (nine prospective, four retrospective) reported on defined objective response rate (ORR). Escalated-dose SSA, in general, was associated with a significant likelihood of disease control but not disease regression. Reported disease control rates (DCR) ranged from 4 to 100%; however, the lowest rate of 4% was noted in a study of 28 patients from 1996 that investigated short-acting octreotide (rather than octreotide LAR) and did not use RECIST criteria. When this outlier was excluded, DCR ranged from 30 to 100%. In contrast, escalated-dose SSA produced universally modest response rates. When studies reported prior to 2002, which used short-acting SSA and non-RECIST response criteria (such as WHO), were excluded, objective response rates (ORR) ranged from 0 to 14%. The study with the highest response rate [37] only included 14 patients, and thus this response rate should be interpreted with caution.

OS and PFS

In general, OS is a challenging endpoint in NETs, regardless of the investigational agent, due to prolonged survival times often associated with multiple lines of therapy, as well as the heterogeneity of the disease. OS is not often used as a primary endpoint in NET trials due to the long survival of many patients with NET [41].

OS was reported in only three studies. The 1-year OS was 88% in Chadha 2009 [39]; median survival was 22 months in Di Bartolomeo 1996 [33] and 36.3 months in Shen 2016 [35]. These numbers are difficult to place in context given the heterogeneity inherent in NET outcomes and the differences in the populations enrolled in each study. For example, Chadha was a retrospective single tertiary referral centre review, Di Bartolomeo was a prospective multicentre trial in Italy enrolling patients with progressive disease and Shen analysed patients from the SEER database above 65 years of age with a diagnosis of NETs.

Similarly, PFS was only reported in four studies. Median PFS was 6.8 months in Wolin 2015 [26], 8.4 in Strosberg 2017 [7], 30 in Ferolla 2012 [27], and 32 in Modica 2015 [36]. Like OS, the wide variation is also likely due to differences in the baseline trial populations and histological grade, as well as variations in the dose of SSA administered.

Biochemical response and symptomatic improvement

Biochemical response rates were only reported in eight studies, of which six utilized both plasma CgA and urinary 5-HIAA, whereas the remaining two used urinary 5-HIAA only. Biochemical response was defined as a decrease in the marker of >50% in four of the eight studies [28, 30, 31, 33], >10% in one study [20], and no specific cut-off was set in the other three studies. Response rates ranged from 23 to 100%. Interestingly, Al-Efraij 2015 reported the lowest response rates (23% for urinary 5-HIAA, 31% for CgA) despite requiring a smaller change in markers to qualify as a response [20].

Ten studies (six prospective, four retrospective) reported on the effect of escalated-dose SSA on symptomatic improvement. No studies used pre-validated scales to assess

the severity of symptoms. Those studies reporting on change of symptom severity using serial analogue scales used different scale ranges (for example, 0–3 [29] and 0–5 [27]). Three studies, Anthony 1993, Eriksson 1997 and Faiss 1999, reported the results of the cohort as a whole; significant improvement in flushing was demonstrated in the first two studies and significant improvement in diarrhoea in the third [29, 30, 34].

The other seven studies reported the percentage of patients who experienced symptomatic improvement. Symptom scores in Ferolla et al. 2012, CTCAE criteria applied to NET symptoms in Al Efraij et al. 2015, symptom frequency in Wolin et al. 2015 and a combination of symptom frequency and intensity in Di Bartolomeo et al. 1996 were used as endpoints to describe symptom improvement. Three studies did not describe the objective system used to determine symptom improvement [19, 36, 37]. Rates of symptom improvement in these eight studies ranged from 27 to 100%, although the studies investigated small numbers of patients (the one study reporting 100% symptomatic improvement enrolled 28 patients). With respect to specific symptoms reported in other studies, rates ranged from 27 to 79% for improvement in diarrhoea (Wolin 2015, Strosberg 2014) and from 81 to 91% for reduction in flushing (Strosberg 2014, Al Efraij 2015).

Toxicity

Rates of toxicity were reported in 11 studies. Escalated-dose SSA was generally well tolerated. Discontinuation rates were reported by one study investigating lanreotide from 3 to 12 mg/day (that is, 84–336 mg/month) at 21% as a result of cholelithiasis and diarrhoea [31]. The incidence of any adverse event ranged from 15 to 40%. The most common toxicities were abdominal discomfort (4–5%), cholelithiasis (3–5%), injection site discomfort (2–5%) and fatigue (up to 30% in Faiss et al. 1999). As no studies included a comparison arm, we could not comment on the incremental toxicity of dose escalation compared to standard dose SSA.

Discussion

Summary of evidence

Dose-escalated SSAs are often used in the management of NET patients in the real world, despite the lack of randomized evidence to support this strategy. Most commonly this is used to control symptoms of hormonal excess in patients with functional NETs, given the lack of other proven options. The use of escalated-dose SSA for the primary aim of tumour control is more controversial. Clinicians may consider increasing the dose of non-toxic SSAs rather than progress to other proven systemic therapies, such as everolimus [6], sunitinib [4] and PRRT [7], largely due to the significant toxicity of targeted agents and the logistics involved in organizing PRRT. Furthermore, if escalated-dose SSA was effective in tumour control, this could present an effective long-term option, which could delay the initiation of subsequent therapies with continued preservation of quality of life.

This systematic review identified 18 trials enrolling 1002 patients. As expected, significant heterogeneity was present —including in trial design (retrospective vs. prospective), site of primary (unspecified vs. bronchial vs. GEPNET), SSA used (octreotide vs. lanreotide) and dosages employed. Another important difference was the requirement for prior administration of standard-dose SSA therapy. While four studies did not mandate the prior use of SSAs, these studies were published more than 10 years ago, in the era when the antiproliferative properties of SSAs were less well recognized. The prior use of SSAs has the potential to alter disease biology, as well as altering the pharmacokinetics of SSAs [42], thus potentially resulting in a smaller clinical benefit of de novo high-dose SSA (whether measured by rate of objective tumour response or symptomatic benefit). Given the heterogeneity in studies, meta-analysis is not an appropriate strategy to analyse the extracted data, with systematic review being the better way to summarize the evidence.

We elected to exclude trials of pasireotide from our systematic review as no “standard” dose has been established in the clinical setting, although two dose-escalation trials were identified by the literature search [43, 44].

Although two randomized controlled trials were included in this review (Strosberg et al. 2017, Wolin et al. 2015), both compared escalated-dose SSA to therapy other than standard-dose SSA. Consequently, it is difficult to estimate the true benefit of escalated-dose SSAs. While the remaining studies were well conducted, their single-arm nature precluded an assessment of low risk of bias, and the outcomes of symptomatic relief and toxicity were judged to be at high risk of bias due to potential measurement bias. In addition, most studies did not report results by histological grade, which is a well-recognized prognostic and predictive factor. While disease control was shown to occur with high-dose SSA treatment in the majority of patients, actual objective tumour response was uncommon. However, given the natural history particularly of low-grade NET, disease stability is a worthwhile outcome in many patients, especially if treatment is well tolerated. Escalated-dose SSA would not be likely to yield benefit where tumour burden or location produces significant symptoms, such as rapidly progressive disease, local obstruction or compression of vital structures.

Escalated-dose SSA is associated with an acceptable safety profile. All included studies reported low rates of significant toxicity, whether patients had been pre-treated with SSAs or not. The profile of side effects—gastrointestinal discomfort, cholelithiasis, fatigue—was similar to that noted with conventional-dose SSAs in large randomized trials [2, 3], without new safety signals of concern. Case reports were identified in the literature search, which described a patient with insulinoma experiencing worsened hypoglycaemia on SSA escalation [45] and a case series of patients who experienced worsened diarrhoea due to potential pancreatic insufficiency [46], but these were excluded from formal review as less than five patients were included in each report.

This systematic review has several strengths. A comprehensive search strategy and risk of bias assessment provides confidence that all available published data to date have been evaluated rigorously according to objective criteria. Previous systematic reviews were flawed by focussing on the benefit of one SSA only, or including expert opinion as part of the search strategy; additionally, there was no systematic report of data for biochemical or symptom control [23, 24]. The meta-analysis published in 2012 investigating the anti-tumour effect of SSAs [47] included only prospective studies and included all SSA dosages. However, 24 of the 28 studies would be ineligible for this systematic review because SSAs were administered either at or below the standard dose. In comparison, this study specifically focuses on the question of dose-escalated SSA, with most studies requiring disease progression or increase in carcinoid symptoms on standard-dose SSA. One other systematic review from 2013 [48] identified 18 studies of high-dose octreotide only specifically in the setting of carcinoid crisis and concluded that short-acting octreotide was of value in this setting, although the timeframe of administration (hours to days) means that assessment of their long-term anti-tumour efficacy is not possible.

Limitations of the current review include the small number of patients accrued in individual trials, the heterogeneous patient populations and interventions investigated, and the single-arm methodology of most trials. This explains the wide variance in results, but also limits accurate assessment of true benefit. These limitations have arisen from the paucity of high-quality evidence available to answer the clinical question, rather than the methodology used in conducting this review. Ideally, access to individual patient data would have facilitated a more accurate assessment of outcomes; however, this is a huge undertaking, particularly when several studies were conducted many years ago. In addition, we opted to include the first dose-escalation episode for each patient to facilitate analysis. Although this could have introduced a bias into our review by excluding future dose-escalation events, the only paper that reported the result of second (and subsequent) dose escalations was Strosberg 2014, which reported the effect on NET symptoms, with no significant difference in efficacy rates. Therefore, this aspect of the study design did not significantly affect the reported results.

This review gives a robust platform to justify prospective randomized trials of dose escalation of the SSA class of therapy. CLARINET FORTE (NCT02651987) is a phase II, single-arm trial investigating dose escalation of lanreotide (120 mg every 14 days) in patients with well-differentiated NETs who progress on standard-dose treatment; the study is scheduled to be completed in late 2019, and will provide further evidence in this area. Future trials should examine the effect of higher dose and/or increased frequency to improve symptom control, where SSAs could be compared to newer agents such as telotristat, which specifically blocks the serotonin production pathway through inhibition of tryptophan hydroxylase. Similarly, prospective randomized controlled trials measuring the anti-proliferative effect of high-dose SSA, with one of the targeted systemic therapies as the standard arm, should be both informative and feasible if well designed and undertaken by cooperative groups, such as the newly formed Commonwealth NET Research Collaboration (CommNETS), or by international scientific societies, such as European NeuroEndocrine Tumors Society (ENETS) or North America NeuroEndocrine Tumors Society (NANETS).

An anticipated benefit of such a trial would be reduced toxicity from treatment with high-dose SSA as compared to targeted agents or chemotherapy, thus underscoring the importance of including HR-QOL as an endpoint for such trials. In addition, trials should formally measure cost effectiveness as well as health system resource utilization of escalated-dose SSA. Finally, in an era of patient-centred care, it is quite possible that patients may prefer a simple treatment, such as SSAs, over a costlier and often more toxic alternate treatment. Patient experience, financial implications, as well as patient preference are important factors that should be assessed with high-dose SSA. Clearly, in disease such as NETs, with generally long survival times, minimizing the impact of treatment on patients' lives is of utmost importance.

The pharmacokinetics of high-dose SSA remains poorly understood. Translational research questions, including understanding the mechanisms of resistance to SSA therapy and the evolution of tumour heterogeneity in metastases, should be linked to high-quality clinical outcome data. The success of recent large randomized controlled trials in the NET population has changed the paradigm for answering clinical questions in this disease. This systematic review supports the need for such studies to advance the care of NET patients through definitive evaluation of the strategy of SSA dose escalation.

Conclusion

The systematic review demonstrates that escalated-dose SSAs is well tolerated in patients with NETs and leads to a significant rate of disease control. The benefit of escalated-dose SSA on tumour response, as well as its impacts on PFS, OS and symptomatic/biochemical improvement, is difficult to judge from current evidence, largely due to the heterogeneity of patient population and study design in published studies. Based on this systematic analysis, a strong case can be made for large, prospective studies investigating the role of escalated-dose SSA in treatment of metastatic NET.

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Compliance with ethical standards

Conflict of interest DLC has received travel support from Novartis and honoraria from Ipsen. DF has received honoraria and research funding by Novartis, Ipsen and Pfizer. MA has received honoraria and travel support by Novartis and Ipsen. NP has received speaking honoraria and travel grant support from Roche, Amgen and Sanofi-Aventis, sat on advisory boards for Roche, AlphaPharm, Amgen and Sanofi-Aventis, and received research funding from Sanofi-Aventis. ES has received honoraria from Roche, Bayer, Ipsen and Pfizer, research funding from Merck Serono and Ipsen, and travel support from Roche and Ipsen. SS has received honoraria and travel funding from Ipsen, Pfizer and Novartis.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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