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Response and relapse rates after treatment with long-acting somatostatin analogs in multifocal or recurrent type-1 gastric carcinoids: A systematic review and meta-analysis

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Abstract

Background: Type-1 gastric neuroendocrine tumors represent a recurring disease and long-acting somatostatin analogs can inhibit both gastrin release and endocrine cell proliferation. The efficacy and timing of this treatment are still unclear. We performed a systematic review of the literature to clarify the role of somatostatin analog treatment in type-1 gastric neuroendocrine tumors.

Methods: A computerized literature search was performed using relevant keywords to identify all the pertinent articles published in the last 15 years.

Results: Eight studies were included in this systematic review on somatostatin analogs in type-1 gastric neuroendocrine tumors. A complete response rate ranged from 25–100%. When only the six prospective studies were considered, no significant heterogeneity was observed, and the pooled cumulative complete response rate was 84.5% (confidence interval 73.8–92.8). Three studies evaluated the type-1 gastric neuroendocrine tumor recurrence, with a cumulative relapse rate of 30.2% (confidence interval 13.1–50.6) after 34 months.

Conclusion: Somatostatin analogs, namely lanreotide and octreotide, have an excellent response rate, with a good safety profile in selected type-1 gastric neuroendocrine tumors, which cannot be safely managed by endoscopic follow-up or resection due to multiple or frequently recurring disease. After therapy discontinuation, the cumulative relapse rate observed after a median 34-month follow-up was relatively high (30.2%).

Keywords

Gastric neuroendocrine tumors, gastric carcinoids, somatostatin analogs, lanreotide, octreotide

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Introduction

Gastric carcinoids or gastric neuroendocrine tumors (gNETs) account for 8.7–23% of all digestive neuroendocrine neoplasms (NENs).[1–3] Their incidence has shown a 7–10-fold increase over the past few decades.[4–8] Type-1 gNETs (gNET-1s), the most common NETs of the stomach,[9] are associated with chronic autoimmune atrophic gastritis and hypergastrinemia. Hypergastrinemia, which is the result of atrophic gastritis, has been shown to stimulate the growth of epithelial cells and prevent apoptosis, possibly contributing to increased cancer risk, including type 1 gastric

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carcinoids.[10] Furthermore, gNET-1 might also develop as a result of hypergastrinemia due to long-standing *Helicobacter Pylori*-related atrophic body gastritis.

gNET-1, which are more common in women and tend to occur after the fifth decade of life,[11–13] are mainly benign; metastatic forms are rarely reported.[14–18] A tumor size > 10 mm is proposed by European NeuroEndocrine Tumor Society (ENETS) guidelines as the cut-off diameter to identify tumors with more aggressive behavior that deserve radical resection and/or a more intensive follow-up program.[3] In a recent multicenter Italian study, including 156 gNETs, a tumor size >10 mm was significantly associated with potentially malignant tumor behavior, irrespective of Ki67.[19]

The clinical management and treatment of gNET-1s are a matter of debate as they are relatively benign lesions,[9,12,20] therefore minimally invasive procedures are warranted. Small (≤1 cm) localized tumors should be endoscopically resected.[3,21–24] With larger lesions, endoscopic mucosal resection or endoscopic submucosal dissection (ESD) can be used to maximize complete endoscopic resection rates,[3,20,23,25] if there is no muscularis propria invasion.[20,26–28] Surgical resection is generally recommended in the case of involvement of the muscularis propria and/or local lymph nodes documented by ultrasound endoscopy.[3,20,26]

However, gNET-1s often represent a multifocal and recurring disease and, in cases of multiple (≥6 lesions), recurrent, partially invasive (beyond submucosa), > 2 cm sized tumors, guidelines are lacking and not as univocal. In addition, the cut-off of six tumors proposed by ENETS is not clearly based on solid scientific evidence. Antrectomy has been suggested to achieve gastrin suppression;[3,29] however, data are scanty[30] and recurrence might still happen.[31,32] Therefore, antrectomy plays a negligible role and seems no longer justified, especially considering the risk of surgery and the potential risk of developing adenocarcinoma in the remaining gastric mucosa.

Long-acting somatostatin analogs (SSAs) can be used to both inhibit gastrin release and directly inhibit endocrine cell proliferation.[6,9,19,33–40] SSA therapy can reduce and even normalize the gastrin and chromogranin A (CgA) levels as well as induce regression of gNET-1,[19,41,42] thus represent a valid therapeutic option. A high recurrence rate after the end of treatment has been reported,[20] which makes the efficacy of this treatment questionable. Whether treatment should be continued in the long term[36,39] or discontinued after 1 year[33–35,37,38] is unclear.

We performed a systematic review of the literature to clarify the role of SSA treatment in complex cases of gNET-1 and define its perfect timing.

Methods

A computerized literature search was performed in PubMed, Embase, SCOPUS, and Web of Science using both free language words and phrases and medical subject heading terms including: gastric carcinoids type 1; gastric neuroendocrine tumors; gastric neuroendocrine neoplasm; chronic atrophic gastritis; somatostatin analogs; treatment; therapy; follow-up, with the search strategy updated last on March 2019. For "disease condition", the following terms were used: (gastric) AND (neuroendocrine OR endocrine) AND (tumor OR tumour OR neoplasm) OR (carcinoid). The search also included the following terms for "therapy": lanreotide OR octreotide OR somatostatin AND analogs OR analogues. The reference lists from the studies selected by the electronic search were then manually searched to identify further relevant reports. All the available primary studies, review articles, abstracts and proceedings of relevant meetings were considered, whereas non-English language papers were excluded. The studies considered potentially eligible were retrieved as full text and evaluated. Disagreements were resolved by consensus.

Study selection criteria

Eligible studies investigated the use of octreotide or lanreotide in patients with histologically confirmed gNENs and clearly classified as gNET-1s. Both retrospective and prospective studies were included; single-arm studies were also eligible. Indications to start SSA therapy had to be clearly specified, due to multifocal disease (≥6 lesions), invasive (beyond submucosa), > 2 cm-sized tumors or recurrent disease. The dosage and type of SSAs had to be specified and studies in which SSAs were used at no standard dose were excluded. A minimum of 12 months of follow-up after therapy discontinuation was considered adequate. Follow-up was defined as the time between the end of treatment and the time of the last observation. In this phase, both a possible recurrence of the gNET-1 and any possible treatment side effects were monitored.

Assessment of the quality of the studies

All the studies included were evaluated for their methodological quality, considering their study design (cohort studies or case series), patient selection (consecutive or non-consecutive), data collection (prospective, retrospective or unknown), spectrum composition (reflecting, or not, the representativeness of the patients of the clinical practice), according with previously defined standards.[43,44]

Outcome measures

The primary endpoints were both the response rate and recurrence-free survival to evaluate the efficacy of SSAs in the treatment of "high risk" gNET-1. Secondary endpoints were biochemical response and toxicity of SSAs to establish the SSA treatment safety.

Methods of the review of the literature

Two reviewers (SM and RER) evaluated all the studies identified as described above: each paper was re-examined to confirm those fulfilling the inclusion criteria and then graded on their methodological quality, based on previously reported criteria.[43,44] The data concerning the types of participants and outcome measures were independently extracted by the reviewers, who openly discussed any discrepancies. Only in the case of disagreement was the further and definitive judgment of an independent clinical expert (PI) applied.

The excluded studies and the reasons for exclusion were recorded. In the case of duplicate publications, the most up-to-date version was considered.

Statistical analysis

Demographic characteristics, complete response rates and relapse rates were taken from each study and exact 95% confidence intervals (CI) were calculated based on a binomial distribution. Given the poor methodological quality of most of the papers retrieved, a more conservative model of random effects to pool the estimates of outcome measures was used, even when there was no significant heterogeneity.[45] To test the inconsistency of the study results, the I^2 statistic was used, indicating the percentage of variation among studies due to heterogeneity rather than chance. A meta-analysis was performed only in the case of no statistical heterogeneity among studies. All the statistical analyses were performed by using MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium).

Results

A total of 1994 studies were identified. After filtering for English language, human studies, year range, article type, and removing duplicates, 31 articles were considered. Out of these, only eight studies[18,33–35,37,39,40,46] fulfilled inclusion criteria for the current systematic review as containing pertinent data. No randomized clinical trials were found; therefore, a meta-analysis of nonrandomized studies was done. Figure 1 represents the study selection process in the PRISMA diagram. Eight studies were included in the current systematic review, with a total number of 117 patients studied (Table 1). None of the studies were sponsored by any organization. Six studies were prospective[33–35,37,39,46] and two retrospective.[18,40] Four studies[34,35,37,39] investigated octreotide, three involved both lanreotide and octreotide,[33,40,46] whereas the type of SSA was not specified in one study only.[18] The SSA used and the dosage applied also varied among the studies. Doses used for octreotide ranged from 20 mg to 30 mg over 28 days; in the three studies using lanreotide, the doses utilized ranged from 60 mg to 120 mg over 4 weeks.[33,40,46]

Considering all the studies, a complete response rate after 12 months on SSA therapy ranged from 25% to 100%. No meta-analysis was performed because of the significant heterogeneity of the studies. The study with the highest response rate[39] only included three patients, and thus this response rate should be interpreted with caution. The larger retrospective study was Italian and multicenter by Campana et al.[40] that included 97 gNET-1s, for which 36 patients were treated with SSAs. SSA therapy resulted in a complete response for 76% of patients and in stable disease for 24%. A prolonged period of therapy (17 months or longer), the use of a full dose of SSAs (lanreotide Autogel 120 mg or octreotide LAR 30 mg every 28 days) and higher gastrin levels at diagnosis were related to a complete response to therapy. The larger prospective study was by Grozinsky-Glasberg et al.,[33] including 15 patients with gNET-1 treated with monthly long-acting release octreotide (20–30 mg; $n = 14$) or lanreotide 90 mg ($n = 1$) for at least 6 months, in which the authors reported a complete tumor disappearance at 1 year of treatment in 11 patients (73%), whereas in three patients (20%), the tumors decreased significantly in number and size.

When only the six prospective studies (49 patients) were considered, no significant heterogeneity was observed, thus they were pooled in the final meta-analysis and the cumulative complete response rate was 84.5% (95% CI 73.8–92.8) (Figure 2).

In terms of treatment duration, no clear-cut data are available. The majority of authors have suggested a treatment period of at least 12 months.[33–35,39,46]

Three studies[37,39,46] evaluated the relapse rate. No significant statistical heterogeneity was observed and from the meta-analysis performed, a cumulative relapse rate of 30.2% (95% CI 13.1–50.6) after 34 months was observed (Figure 3). A small Norwegian prospective study by Jianu et al.[37] analyzed the macroscopic and histopathological changes in the stomach of five gNET-1 patients 5 years after discontinuation of octreotide previously taken for 1 year. The authors reported that the disease had progressed in all five gNET-1

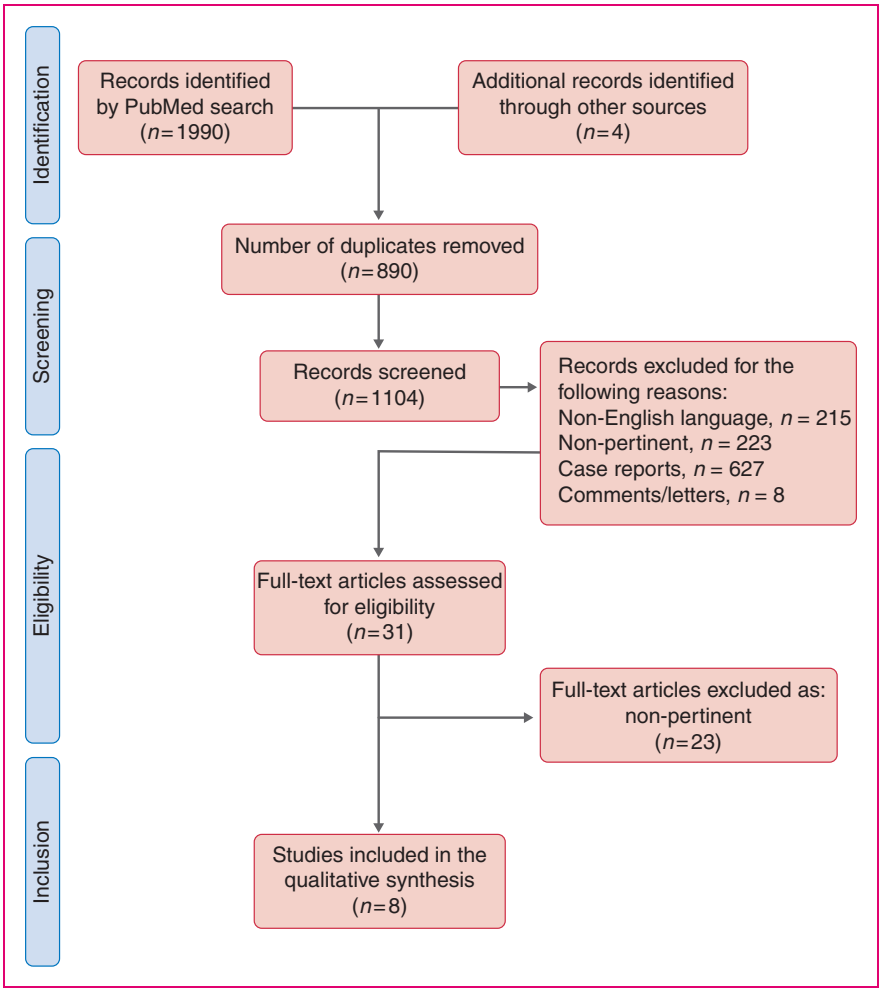

Figure 1. Flowchart of the study selection process.

Table 1. Summary of the results of the eight studies evaluating SSAs in gNEN-1 and included in the systematic review.

Author	Year	Type of study	No. pts	gNEN-1	Intervention	Schedule	Complete response at 12 m (%)	Follow up (*m*)	Recurrence (%)
Massironi[46]	2015	Pros	12	Recurrent gNEN-1	Octreo 30 mg i.m., lanreo 120 mg i.m.	every 28 days For 12 m	92	46.5	33 at 20m
Khuroo[39]	2010	Pros	3	gNEN-1	Octreo 20 mg i.m.	every 28 days For 12 m	100	34	0 at 34m
Grosinski[33]	2008	Pros	15	gNEN-1	Octreo 20/30 mg i.m.	every 28 days Long-term	73	18	NA
Campana[34]	2008	Pros	9	Multiple gNEN-1 > 5mm	Octreo 30 mg i.m.	every 28 days For 12 m	100	12	NA
Fykse[35]	2004	Pros	5	gNEN-1	Octreo 20 mg i.m.	every 28 days For 12 m	80	12	NA
Jianu[37]	2011	Pros	5	gNEN-1	Octreo 20 mg i.m.	every 28 days For 12 m	80	84	40 at 60m
Thomas[18]	2013	Retro	32	gNEN (G1-2) Type not specified	SSA not further specified	NA	25	39.5	NA
Campana[40]	2016	Retro	36	gNEN (G1-2) Type not specified	Octreo 30/20 mg or lanreo 60/120 mg	every 28 days long term	76	NA	NA

i.m.: intramuscular; gNEN1: gastric neuroendocrine neoplasm type 1; lanreo: lanreotide; octreo: octreotide; pros: prospective; retro: retrospective; SSA: somatostatin analog.

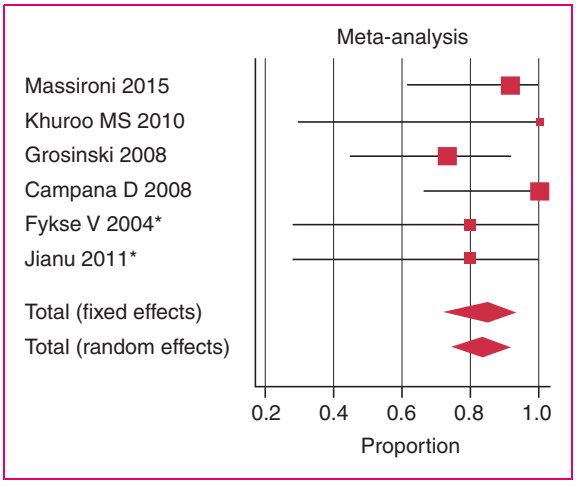

Figure 2. Forest plot of the prospective studies considered for the final meta-analysis in which the cumulative complete response rate to somatostatin analogs (SSAs) was 84.5% (95% confidence interval 73.8–92.8).

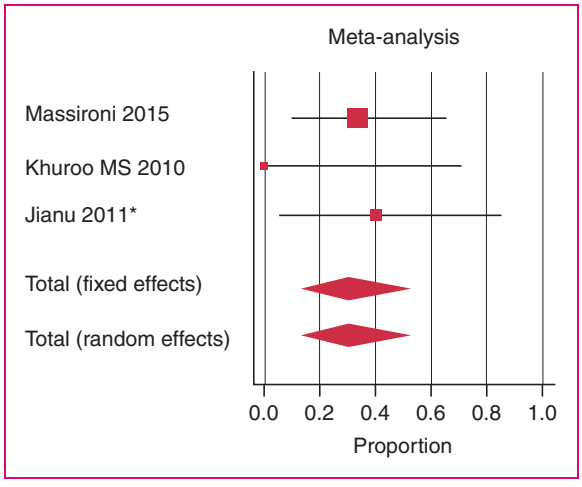

Figure 3. Forest plot of the three studies that evaluated the relapse rate, showing the cumulative relapse rate of 30.2% (95% confidence interval 13.1–50.6) after 34 months.

patients: one patient had a highly malignant gastric tumor, one had an increased number of gNET-1 with regional and distant metastases, and three had an increased number of gNET-1s.

For the adverse events rate, the rates of toxicity were reported in seven studies.[18,33–35,37,39,46] Considering the prospective studies, this ranged from nil to 88%, because of the different attention paid to adverse events. In the study reporting 88% of adverse events, intestinal bloating was the main symptom reported in eight out of nine patients,[34] but when considering clinically significant adverse events, the rate varies from 2% to 8%, thus confirming the safety profile of the SSAs. The most common toxicities were abdominal discomfort,[34] cholelithiasis,[46] diarrhea[35,37] and fatigue or weight loss.[35]

Biochemical response rates were reported in six studies[18,33–35,39,46] in which a reduction in both circulating CgA and gastrin levels was observed. The extent of the reduction was greater than 50% of the baseline values in all the studies in which it was evaluated, therefore among these studies, the biochemical response was observed in 100% of cases. The remaining two studies did not report any information about biochemical data.[37,40]

Discussion

According to the present study, in selected cases that cannot be safely managed by endoscopic follow-up or resection due to multiple or frequently recurring disease, SSAs have shown an excellent response rate (i.e. a cumulative complete response rate of 84.5% when considering the six prospective studies) after 12 months on therapy, with a good safety profile.

The use of SSA therapy in gNET-1s is still a matter of debate. Therapeutic strategies for gNET-1s are based on risk stratification according to tumor size, lesion number, stage, and grade.[14,18,34,41,47] According to the current guidelines from the ENETS, endoscopic management with lesion resection[3] represents the gold standard for gNET-1s that do not infiltrate the muscularis propria and with no evidence of angioinvasion, whereas surgery should be limited to cases of clearly demonstrated invasion beyond the submucosa and/or with metastases. In cases of multiple ($\geq$6 lesions), recurrent, partially invasive (beyond submucosa), $>$2 cm-sized tumors, guidelines are lacking and not so univocal. Furthermore, the cut-off of six tumors proposed by ENETS is not clearly based on solid scientific evidence. The results of this meta-analysis can complete these areas of uncertainty. In light of our results, far from being the first-line therapy for gNET-1s, SSAs may represent a valid option in those complex cases that, due the disease being recurrent, multifocal, or the polyps are fewer than six in number, an endoscopic therapy is not feasible and the alternative treatment remains the surgical resection of the lesions associated with surgical antrectomy. In this specific patient setting, the evidence obtained from our meta-analysis supports the use of SSAs.

Once therapy was discontinued and after a median 34-month follow-up, the cumulative relapse rate observed was relatively high (30.2%). Campana et al.[40] observed that in patients with gNET-1s at stages 0–2A, a disease recurrence of 26.3% was observed in patients treated with SSAs and in 26.2% of patients treated with endoscopic resection, with no

statistically significant difference in terms of disease-free survival. Prolonged medical therapy (17 months or longer) was reported to be the only predictor of disease recurrence.

Recurrence after presumed successful treatment is common because hypergastrinemia and underlying Enterochromaffin-like (ECL) cells hyperplastic or dysplastic changes persist, as high as 65% within a year after initial endoscopic treatment.[19,22] Additionally, the recurrence rate is likely to be affected by the type of endoscopic procedure used to remove the neoplastic lesions,[14,48] as confirmed by the lower recurrence rates reported by Japanese studies, where the use of ESD is more common compared to standard polypectomy.[21]

The surgical approach, either antrectomy to achieve gastrin suppression or partial/total gastrectomy, was more common in the past and probably represented an over-treatment for this subset of relatively indolent tumors, also considering both the risk of surgery as well as the potential risk of developing adenocarcinoma in the remaining mucosa. In the retrospective study by Thomas et al.,[18] a 65% complete response rate was observed in surgically treated patients, which was lower when compared to previous data.[49] A few cases of recurrence even after surgery have been reported.[31]

In multiple and recurrent disease, SSAs can be therefore a viable therapeutic option instead of antrectomy. The rationale for the use of SSAs is based on the relatively indolent nature of these tumors and the SSA action of both inhibiting gastrin secretion from G cells and exerting an anti-proliferative effect on the ECL cells.[26,46,47]

Treatment is generally well tolerated, although some adverse effects have been reported, including abdominal pain with cramps, constipation, diarrhea, steatorrhea, injection site irritation and local pain, nausea and vomiting. Hypothyroidism, cholecystitis, and cholelithiasis, acute pancreatitis, alopecia, acute hepatitis, hyperbilirubinemia, hyperglycemia, hypoglycemia, and prolonged QT intervals are less common but are still possible complications.[50,51] The SSA good safety profile has been confirmed by the present study, as no serious adverse events were reported by the included studies, except for one patient developing cholelithiasis.

The precise duration of SSA treatment has not yet been defined and, considering the relative indolent nature of these tumors, the length of treatment needs to be balanced with costs and possible side effects including the risk of cholelithiasis, diarrhea, abdominal discomfort and diabetes. However, a longer duration appears to be related to lower recurrence rates.[40] Furthermore, the subgroup of gNET-1 patients that would benefit most from SSA treatment needs greater clarification. According to the current evidence, SSA therapy can be considered for patients with multiple and highly recurrent tumors that are not amenable to surgical treatment,[26] or even instead of surgery, which is poorly justified in this kind of relatively indolent tumor.

A possible limitation of the present study is that this is a meta-analysis of nonrandomized studies and the application of formal meta-analytic methods has been controversial.[45] One reason for this has been that potential biases related to the extreme diversity of study designs and populations in epidemiology make the interpretation of simple summaries problematic. Another possible limitation is the small number of included studies, especially those evaluating the relapse rate, of which there were only three.[37,39,46] Moreover, the number of patients included in each study was small and the required sample size was not calculated. In addition, methodological issues related specifically to meta-analysis, such as publication bias, could have a particular impact when combining the results of nonrandomized studies. In contrast, no statistical heterogeneity among studies was present when considering only the six prospective studies,[33–35,37,39,46] which represents a point of strength for our study.

In summary, SSA therapy can be considered a viable option for gNET-1s, although in those selected cases that cannot be safely managed by endoscopic follow-up or resection due multiple or recurrent disease, as SSA therapy has shown an excellent response rate with a good safety profile. Further prospective studies are warranted to draw a more robust conclusion, especially for the precise duration of treatment to reduce the percentage rate of tumor recurrence. The identification of specific prognostic markers that can identify the subset of gNET-1 patients with more aggressive features, thus deserving more radical treatment, also needs to be addressed in future studies.

Author Contributions

SM designed the work. RER performed the literature research; RER and SM independently selected the studies for inclusion in the meta-analysis. PI gave his judgment as an independent expert in cases of disagreement between the reviewers. SM analyzed and interpreted the results.
RER was the major contributor in writing the manuscript together with SM. VM and PI critically revised and corrected the final version of the manuscript.
All the authors read and approved the final manuscript.

Declaration of conflicting interests

The authors declare that they have no conflicts of interest.

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