

Treatment of the carcinoid syndrome with the longacting somatostatin analogue lanreotide: a prospective study in 39 patients

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Abstract

Background—Somatostatin analogues effectively control flushing and diarrhoea in patients with the carcinoid syndrome. The octapeptide lanreotide is available in slow release form, which could eliminate the necessity of twice a day injections as with octreotide.

Patients and Methods—39 patients with carcinoid syndrome were included in a prospective multicentre study. Patients received lanreotide 30 mg intramuscularly every 14 days for six months. The number and intensity of flushing episodes and bowel movements, urinary 5 hydroxy-indolacetic acid (5 HIAA) concentrations, and variations of tumour mass were recorded.

Results—After one month of treatment, flushing episodes (median (range)) decreased significantly (3 (0–3–24) episodes per day *v* 1 (0–15), $p=0.04$) and completely resolved in 39% of the patients. A significant decrease was seen in the number of bowel movements and discomfort related to diarrhoea. Urinary 5 HIAA concentrations were unchanged in 57% of the patients and decreased in 18%. After six months of treatment, the actuarial proportions of patients with at least a 50% decrease in the number of flushing episodes and bowel movements were 54% and 56%, respectively. Forty two per cent of the patients who were treated for six months had at least a 50% reduction in 5 HIAA values. No clear signs of regression of tumours were seen in any of the patients. Lanreotide was well tolerated despite transient mild pain or erythema at the injection site in 25% of the patients. Biliary lithiasis appeared in two patients after six months of lanreotide.

Conclusion—Lanreotide, 30 mg intramuscularly every other week, is an effective and convenient treatment in patients with the carcinoid syndrome.

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in 10–60% of the cases depending on the site of the primary tumour.^{2,3}

In general, the carcinoid syndrome, which associates flushing and diarrhoea as the most common symptoms,⁴ is caused by small intestinal tumours. Colonic and appendiceal carcinoid tumours never produce the syndrome and the syndrome is rare with carcinoids originating in the stomach, lung or testes. In patients with liver metastases, various hormones (serotonin, bradykinins, tachykinins) are released into the general circulation but their exact role in the pathophysiology of the carcinoid syndrome remains to be determined. Treatment of the malignant carcinoid syndrome used to be a difficult challenge in patients who despite metastasised disease often had a prolonged life expectancy.⁵ Loperamide, parachlorophenylalanine,⁶ and cyproheptadine⁷ may improve diarrhoea and the last drug may also correct weight loss because of its appetite stimulating effect. However, the side effects of these drugs and their ineffectiveness for flushing make longterm use difficult.

Somatostatin and its stable analogue octreotide inhibit the release of many gut and pancreatic peptides.⁸ Several studies have reported the effectiveness of octreotide in patients with the carcinoid syndrome,^{1,5,8–15} at doses of between 300 and 1500 µg per day, administered in two or three subcutaneous daily injections.

Lanreotide is a recently developed somatostatin analogue.¹⁶ This octapeptide, which is available in slow release form, due to the presence of microspheres containing polylactide-polyglycolide copolymer, could thus eliminate the inconvenience of multiple daily injections. It has proved to be effective in the control of symptoms in patients with acromegaly.¹⁷

The aim of this study was to evaluate the efficacy and tolerability of 30 mg intramuscular injections of lanreotide every other week for six months in patients with the carcinoid syndrome.

Methods

Patients

Male and female patients older than 18 were included in this prospective multicentre study. All patients had a symptomatic non-resectable carcinoid tumour (primary tumour or

Carcinoid tumours are rare (incidence: about 2/100 000 people)¹ and malignancy – that is, mainly, liver metastases – may be encountered

metastases, or both). Patients' general condition was assessed using ECOG performance status: 0, patient able to perform any task; 1: avoids fatiguing activities but able to move; 2: needs occasional help and confined to the bed <50% of the time; 3: unable to take care of himself; in bed >50% of the time; 4: in bed all the time; may require hospitalisation. Pathological confirmation of the endocrine nature of the tumour was obtained in all cases, from the surgical specimen or by fine needle biopsy.

Patients already being treated with a somatostatin analogue (that is, octreotide) first underwent a three day wash out period to assess baseline symptoms. However, according to the study protocol, a 48 hour washout period was sufficient in case of rapid and severe relapse of carcinoid symptoms.

Patients who had received antitumoral treatment within three weeks before inclusion (chemotherapy, chemoembolisation, interferon, radiotherapy) were excluded from the study, as well as those with associated malignant tumours. Pregnant women and patients unable to give informed consent, those with bowel obstruction, or in poor general condition (ECOG performance status higher than 2) were also excluded.

The study protocol was approved by the ethics committee of Lyon Hospitals, France.

Study design

Lanreotide was administered in 30 mg intramuscular injections, every 14 days for six months. Visits were scheduled at inclusion, and after seven days, 15 days, one month ('short-term'), three and six months ('longterm') of treatment. Each visit included a complete physical examination and assessment of carcinoid symptoms (diarrhoea and flushing). The number and intensity of daily flushing episodes (assessed by patients on a 4 point scale: 0, none; 1, mild; 2, moderate; 3, severe) were recorded for the three days preceding the visits, as well as the number of daily bowel movements and the intensity (0-3) of diarrhoea. Side effects of lanreotide were investigated. Blood samples were collected at inclusion, and after one, three, and six months of treatment. Blood cell count, serum glucose, calcium, electrolytes, creatinin, and protein values were measured, as were liver function tests.

Urinary 5 hydroxy-indolacetic acid (5 HIAA) values, the most reliable biological marker in patients with carcinoid syndrome,¹² were determined after a three day appropriate diet (excluding mainly coffee, tea, chocolate, alcohol, bananas, vanilla, walnuts, tomatoes, liver, smoked fish). Normal values were less than 8 mg (42 μ mol) per 24 hour. Variations during lanreotide treatment were recorded as follows: normalisation, a reduction at least 50% compared with baseline, 'no change' (\pm 50% around baseline value), an increase of at least 50%.

Abdominal computed tomography was performed at inclusion and at three and six months

to evaluate the size of the tumours (mainly liver metastases). Tumour variations were assessed according to WHO criteria by measuring the sum of the products of the two greatest perpendicular diameters of the two or three main measurable lesions. An objective response was defined as at least a 50% decrease; a minor response as a 25-50% decrease; no change in the tumour mass as a \pm 25% variation, and progression as at least a 25% increase.

Abdominal ultrasound was performed at the beginning and at the end of the study, to look for biliary lithiasis.

Statistical analysis

The number and intensity of flushing episodes and bowel movements during the first month of lanreotide treatment were compared with pretreatment values with non-parametric paired Wilcoxon test. During longterm treatment, the proportions of patients with improvement in the number (\geq 50% decrease) or the intensity (\geq 1 grade on the 4 point scale) of symptoms, or both, were calculated according to the actuarial method, to consider the results of the patients who dropped out before the end of the study. The number and intensity of these two symptoms at six months or at the last visit (last value carried forward, or LVCF) were compared with pretreatment values with paired *t* test. The statistical significance level was set at $p=0.05$.

Results

Thirty nine patients (24 male, 15 female, mean (SD) age: 63.7 (10.2) years) were included between December 1991 and January 1993. Table I summarises the main patient characteristics. Thirty one patients (79%) presented with diarrhoea and 32 (82%) with flushing episodes; 24 had both. The median (range) number of daily flushing episodes at inclusion was 3 (1-24) and the median intensity was 2 (1-3). The median (range) number of daily bowel movements was 4 (1-15) and the median intensity of diarrhoea was 2 (1-3). Median (range) 5 HIAA urinary concentrations were 50 (3.6-348) mg/24h (normal values <8 mg/24 h).

TABLE I Main characteristics of 39 patients with the carcinoid syndrome

	Patients (n)	
Site of primary carcinoid tumours (resected in 31 patients)		
Gut		25
Bronchi		3
Testes		1
Unknown*		10
Metastases		
Liver		36
Lymph nodes		4
Peritoneum		4
Lung		2
None		2
ECOG performance status		
0	10	
1	25	
2	4	
Previous treatments		
Intravenous chemotherapy		16
Octreotide†		16

*Including two patients with apparently isolated liver metastases.

†Mean dose: 410 μ g/day for 21 (0.5-82) months.

TABLE II Number and intensity (median and range) of daily flushing episodes and bowel movements before and after seven, 15, and 30 days of treatment with lanreotide, 30 mg intramuscularly every other week in patients with the carcinoid syndrome

	Before lanreotide	Day 7	Day 15	Day 30
Flushing				
Patients (n)	32	31	31	31
Daily episodes (n)	3 (0.3-24)	0.5 (0-10)*	1 (0-16)*	1 (0-15)*
Intensity (0-3)	2 (1-3)	1 (0-3)	1 (0-3)	1 (0-3)
Complete resolution (%)		45	42	39
Diarrhoea				
Patients (n)	31	30	30	31
Daily bowel movements (n)	4 (2-15)	3 (1-7)**	3 (1-6)**	3 (1-7)**
Intensity (0-3)	2 (1-3)	1 (0-3)	1 (0-3)	1 (0-3)
Complete resolution (%)		17	13	30

* $p < 0.05$ v pretreatment value, ** $p < 0.01$.

TABLE III Evolution of 5 HIAA urinary concentrations in 39 patients with carcinoid tumours during one month treatment with lanreotide, 30 mg every other week. Median (range) baseline value was 50 (3.6-348) mg/24 h (normal < 8 mg/24 h)

	Day 7	Day 15	Day 30
>50% decrease (%)	35	22	18
No change (%)	50	56	57
>50% increase (%)	15	22	25

SHORT-TERM RESULTS

Symptoms

Table II shows the evolution of the number of daily flushing episodes and bowel movements within the first month of lanreotide treatment, as well as of the intensity of symptoms.

A significant decrease in the number of flushing episodes was seen after seven ($p < 0.05$), 15 ($p < 0.05$), and 30 days of treatment ($p < 0.05$). Diarrhoea also decreased significantly ($p < 0.01$ at day 7, day 15, and day 30), although complete resolution occurred less often than flushing (Table II).

The intensity of both symptoms significantly decreased at all treatment intervals ($p < 0.001$). The number and intensity of flushing episodes and bowel movements did not significantly differ in patients previously treated with octreotide, compared with those who had never been treated with this somatostatin analogue ($p > 0.1$).

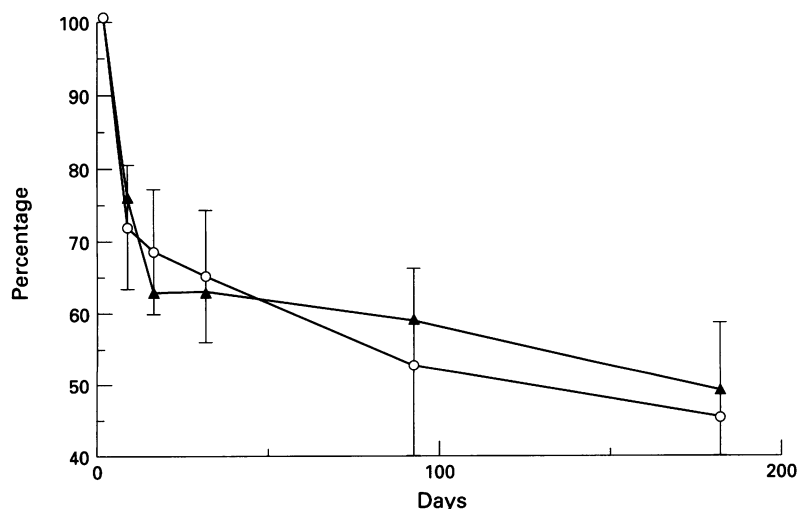


Figure 1: Actuarial curves of patients who did not have at least a 50% decrease in the number of bowel movements ($n=31$, \circ) or in the number of flushing episodes ($n=32$, \blacktriangle) during six month treatment with lanreotide, 30 mg every other week. Bars show standard deviations.

Finally, lanreotide was completely ineffective for carcinoid symptoms in four patients (two with flushing, two with flushing and diarrhoea) who stopped treatment at the end of the first month. One patient resigned at day 7 for personal reasons; one patient died after one month because of a significant increase in liver metastases. Thirty three patients entered the longterm study.

Biological markers

Table III shows the evolution of urinary 5 HIAA concentrations within the first month of treatment.

LONGTERM RESULTS

Drop outs

Nine of 33 patients stopped treatment before the end of the six month period. Two patients died after three months (one from peritoneal carcinomatosis, one from an unrelated cause). Carcinoid syndrome worsened in three patients, who left the study at the end of the third month; tumoral progression and surgical resection of the tumour occurred in one patient each. Finally, two patients left the study for personal reasons.

Symptoms

Patients' weight did not increase significantly (66.2 (17.7) kg at six months, v 64.6 (15.7) kg at inclusion).

Figure 1 shows the actuarial proportions of patients without symptomatic improvement (defined as at least a 50% reduction in the number of flushing episodes and bowel movements) throughout the six month treatment period. A decrease of at least 50% was seen in 53 and 59% of the patients at six months, respectively. The mean (SD) number of flushing episodes decreased from 4.5 (0.7) before treatment to 1.6 (2.9) at LVCF ($p=0.01$). The mean (SD) number of daily bowel movements decreased from 4.8 (3.3) before treatment to 3.2 (2.0) at LVCF ($p=0.01$). A decrease of at least one degree in the intensity of symptoms was seen in 54 and 56% of the patients for flushing and diarrhoea, respectively (Fig 2). Flushing episodes completely resolved in 12 of 31 (39%), 10 of 25 (40%), and 10 of 19 (53%) patients still treated at one, three, and six months respectively; corresponding figures for diarrhoea were nine of 30 (30%), eight of 26 (31%), and eight of 21 (38%).

Urinary 5 HIAA concentrations

Among the 33 patients, 32%, 45%, and 23% had at least 50% decrease, no change or at least 50% increase in the urinary 5 HIAA values at three months, respectively. At six months ($n=24$), 42% had at least 50% decrease, 12% had at least 50% increase, and 46% had stable 5 HIAA values. 5 HIAA values at six months were not significantly different from baseline.

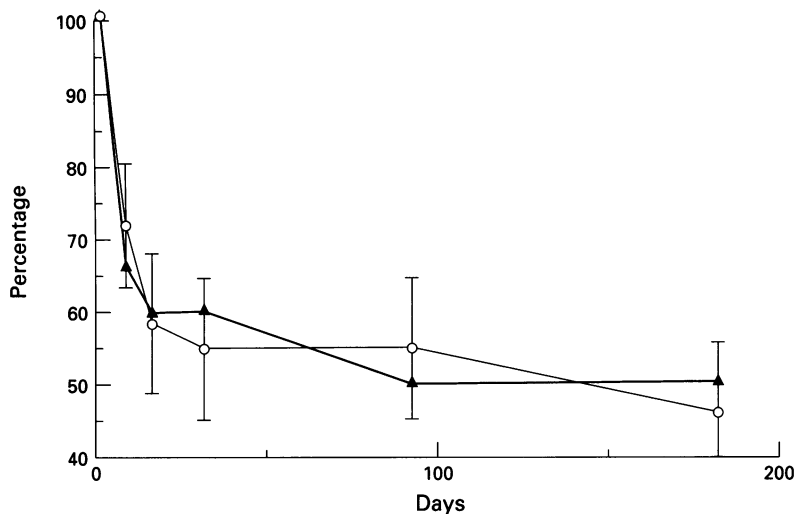


Figure 2: Actuarial curves of patients who did not have at least a 1 point reduction decrease on the 4 point scale (see text) in the intensity of diarrhoea ($n=31$, \circ) or in the intensity of flushing episodes ($n=32$, \blacktriangle) during six month treatment with lanreotide, 30 mg every other week. Bars show standard deviations.

Tumour size

Median (range) tumoral surface was 38.4 (2–165) cm^2 before lanreotide treatment, 26.0 (2–230) cm^2 after three months, and 30.9 (9–187) cm^2 after six months. No objective response was recorded in any patient.

Tolerability

Pain or erythema at the injection site was reported at least once by 25% of the patients. These symptoms tended to disappear after two or three injections, and were judged as 'mild' or 'moderate' in all cases. Four patients reported colic pain or abdominal bloating; transient fever was observed in two patients. A paradoxical increase in diarrhoea for one to three days after the lanreotide injection was seen in three patients. Small bowel obstruction due to peritoneal adhesion led to laparotomy in one patient who had been treated for one month.

Serum glucose values tended to be slightly higher after six months of lanreotide (5.2 (0.6) mmol/l) than before treatment (5.0 (0.8), NS). No other clinically relevant change in blood tests was noticed. Side effects did not lead to treatment discontinuation in any of the patients.

Biliary lithiasis was found on abdominal ultrasound in four of 39 patients before lanreotide, and in two more patients after six months of lanreotide. No symptoms related to lithiasis were seen.

Discussion

Patients with sometimes life threatening manifestations of the carcinoid syndrome, mainly flushing and diarrhoea, have greatly benefited from recent advances in the field of longacting somatostatin analogues. Up to recently octreotide was the only analogue available. Its efficacy for carcinoid symptoms has been shown in several studies. Kvols *et al* have thus showed in 25 patients with the carcinoid syndrome, that octreotide administered in

three daily subcutaneous injections of 150 μg each, resulted in prompt and significant relief from both flushing and diarrhoea.¹² Seventy nine and 76%, respectively of the patients had complete or significant relief from these symptoms at some time in the treatment (best response).

In this study conducted with 30 mg intramuscular of lanreotide, every other week, the number and intensity of flushing episodes decreased significantly within seven days and complete resolution was observed in 40% of the patients during the first month. These figures were maintained throughout the study as indicated by results showing 53% of the patients with at least a 50% decrease in the number of flushing episodes at six months. There are several possible reasons for this rate being slightly lower than those previously reported in studies with octreotide.^{5 11 12} Firstly, a transient decrease in flushing was not defined as a response in our study if subsequent relapse occurred. Moreover, our study protocol did not permit an increase in lanreotide dose during the six month period. Tachyphylaxia has been shown to occur in many patients receiving octreotide, and was even noted in 35 of 51 patients (70%) treated by Janson and Oberg.¹ In our study, some of the patients in whom lanreotide became ineffective and considered as treatment failures might have been controlled by increasing doses of this substance. Although significant, the effect of lanreotide on diarrhoea was less pronounced, at least on the number of daily bowel movements. Complete resolution was less often obtained than for flushing at the beginning of treatment, as previously noted with octreotide by others.⁵ However, the intensity of this symptom decreased very significantly and discomfort was mild during longterm treatment.

The effect of somatostatin analogues on biological markers varies quite widely in the carcinoid syndrome.^{1 5 12 14} It should first be emphasised that, except for serotonin and its urinary metabolite 5 HIAA, which is thought to be responsible for diarrhoea,⁵ the nature of the mediator(s) responsible for the symptoms of this syndrome are not precisely known. Substances like kallikrein, neurotensin, substance P, and prostaglandins may also be involved.⁴ In clinical practice however, urinary 5 HIAA usually serves as an objective indicator of disease activity.¹² In this study, urinary 5 HIAA decreased by at least 50% in only 18–35% of the patients during the first month, and in 42% of the 24 patients still treated at six months. These results do not support those obtained with octreotide by Kvols *et al*, who showed at least a 50% decrease of urinary 5 HIAA concentrations in 72% of 25 patients receiving 150 μg three times daily, and in 64% of those receiving 500 μg three times daily.⁵ Less favourable results have been obtained by others.^{1 12 18} A mean decrease of 5 HIAA by 31 (7%) in nine patients was demonstrated by Souquet *et al*,¹⁴ and a $\geq 50\%$ decrease was found by Janson and Oberg in only 37% of 55 patients.¹ A clear

correlation between the improvement of symptoms and the reduction in urinary 5 HIAA was not found in any of those studies.

Whether tumour regression can be obtained with somatostatin analogues has not been clarified although it has been reported in scattered cases.^{10 19} No objective tumour regression was identified in any patient in this study, in the other study with lanreotide²⁰ or in most studies with octreotide.^{1 14 15} Stabilisation of tumours growing before the beginning of somatostatin treatment has been obtained in 30–50% of the patients with carcinoids or endocrine pancreatic tumours.^{15 21} Although no increase in tumour size was seen in our patients during a six month treatment with lanreotide, the natural slow growth pattern of these tumours should be considered.⁵

Treatment with lanreotide was remarkably well tolerated. Some common and mild side effects, such as pain at injection site and abdominal pain or bloating, have been reported in most studies with octreotide.²² Small bowel obstruction due to peritoneal adhesion occurred in one patient previously operated on. Whether lanreotide was partly responsible for this event previously noted with octreotide²³ cannot be determined. Biliary lithiasis was seen in two of 33 patients, a rate comparable to that seen in other studies.^{1 15 20 24}

Although it was not the aim of this study to compare octreotide and lanreotide, most of the 16 patients previously treated with octreotide appreciated the simplification of the therapeutic regimen with lanreotide and wished to continue the treatment with this analogue. Altogether, the results of this study show that lanreotide, 30 mg intramuscular every other week, is an effective and well tolerated treatment in patients with the carcinoid syndrome.²⁵ Future studies will have to determine whether shortening the interval between two consecutive injections (for example, every 7–10 days) is useful in cases of incomplete control of symptoms or tachyphylaxia. Direct comparisons between octreotide and lanreotide, including efficacy and quality of life parameters as well as the costs of treatments²⁶ are also warranted.

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