Treatment of Carcinoid Syndrome

A Prospective Crossover Evaluation of Lanreotide versus Octreotide in Terms of Efficacy, Patient Acceptability, and Tolerance

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BACKGROUND. The somatostatin analogues lanreotide and octreotide have previously been shown to be effective in controlling flushing and diarrhea in patients with carcinoid syndrome. As lanreotide requires injection only every 10 days, compared with twice-daily injections of octreotide, a direct comparison between these two treatments in terms of patient acceptability, patient preference, and efficacy in controlling symptoms was performed in patients with carcinoid syndrome.

METHODS. Thirty-three patients with carcinoid syndrome were included in an open, multicenter, crossover study. Half of the patients received octreotide 200 μg subcutaneously twice or thrice daily for 1 month followed by lanreotide 30 mg intramuscularly every 10 days for 1 month, while the other half commenced with lanreotide followed by octreotide in a similar fashion. Quality-of-life assessments were performed at each visit and patient preference for one of the two treatments evaluated. The number and intensity of flushing episodes and bowel movements, urinary 5-hydroxyindoleacetic acid (5HIAA) levels, and plasma serotonin levels were recorded.

RESULTS. No significant differences were found between lanreotide and octreotide in terms of quality of life. The majority of patients (68%) preferred lanreotide ($P = 0.03$), largely due to its simplified mode of administration. Disappearance or improvement in flushes occurred in 53.8% of patients (14 of 26) while on lanreotide and in 68% (17 of 25) on octreotide. A disappearance or improvement of diarrhea in 45.4% (10 of 22) on lanreotide, compared with 50% (11 of 22) on octreotide, was also observed. Lanreotide and octreotide were equally effective in reducing urinary 5HIAA levels and plasma serotonin levels. Both treatments were well tolerated, with mild symptoms of abdominal pain and nausea observed in 29% and 14% receiving octreotide and lanreotide, respectively.

CONCLUSIONS. Lanreotide and octreotide are equally efficacious in terms of symptom control and reduction in tumor cell markers for patients with carcinoid syndrome. Due to its simplified mode of administration, most patients prefer treatment with lanreotide. ***Cancer* 2000;88:770–6.**

KEYWORDS: somatostatin analogues, lanreotide, octreotide, carcinoid syndrome, patient preference.

Carcinoid tumors are rare, slowly progressive tumors principally of the lower gastrointestinal tract. The cell of origin is the chromaffin cell, which is part of the amine precursor uptake and decarboxylation system. Thus, these tumors have the ability to secrete vasoactive peptides, mainly serotonin, which is responsible for cutaneous flushing, diarrhea, and bronchospasm, features referred to as the carcinoid syndrome. The occurrence and severity of the syndrome are related

directly to tumor bulk, and its presence almost always implies distant metastases, principally hepatic.

Between 40% and 90% of tumors in patients with carcinoid syndrome are metastatic at the time of presentation,[1,2] and, although hepatic resection, hepatic artery chemoembolization, and systemic chemotherapy may be effective in some patients,[3–10] the mainstay of therapy remains symptomatic control of the carcinoid syndrome with somatostatin analogues.[11] The efficacy of octreotide in controlling symptoms and lowering levels of plasma and urinary serotonin and its metabolites has been well demonstrated.[12–14] However, octreotide has the disadvantage that it requires subcutaneous injection two or three times daily due to its therapeutic short half-life.

Lanreotide is a long-acting somatostatin analogue that requires intramuscular injection two or three times per month and has also been shown to be effective both in controlling symptoms and in reducing tumor markers in patients with carcinoid tumors.[15,16] The treatment of patients with carcinoid syndrome with lanreotide, therefore, would be expected to achieve greater acceptability to patients and to improve quality of life. The objectives of the study were to compare the clinical and biologic efficacy of octreotide and lanreotide in a crossover analysis of patients with symptomatic carcinoid syndrome and to assess both treatment modalities in terms of acceptability to patients and treatment preference.

MATERIALS AND METHODS

Study Design

A prospective, open, comparative study with a crossover design was performed in 35 patients who were enrolled from 15 centers in France. The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of St. Germain-en Laye Hospital. All patients were provided with a detailed explanation of the nature and purpose of the study and possible adverse outcomes, and written, informed consent was given by all patients.

Patient Eligibility

Patients who were eligible for inclusion in the study were those with carcinoid tumors that were confirmed on histologic examination with at least one of the following symptoms: diarrhea (at least 3 stools every 24 hours) or flushes (at least 1 flush every 24 hours). The patients who were enrolled included those who had not been treated previously with somatostatin analogues or who had discontinued their treatment for a sufficient time to allow the reappearance of clinical symptoms (a minimum of 3 stools or 1 flush every 24 hours). Patients with symptoms of bowel obstruction or those for whom surgery for the tumor or its metastases was scheduled in the 3 months after inclusion were excluded. The use of antidiarrhea agents was prohibited during the study period. Patients were withdrawn from the study if they developed symptoms of bowel obstruction or if they required another specific form of therapy for their disease (e.g., radiotherapy, chemotherapy, immunotherapy, or chemoembolization).

Treatment Schedule

Patients were randomized into two groups. Those in Group A were treated with octreotide (200 μg subcutaneously twice or thrice daily) for 30 days (Period 1) followed by lanreotide (30 mg intramuscularly every 10 days on Days 1, 10, and 20) for 30 days (Period 2). Octreotide doses were commenced at 200 μg subcutaneously twice daily and increased to 200 μg thrice daily on Day 5 when no improvement in symptoms was observed. Patients who previously had been treated successfully using doses $>$ 200 μg twice daily started their individually efficacious daily dose regimens. A wash-out period of at least 3 days was applied between the two treatment groups, therefore allowing at least 3 days of wash-out for octreotide and at least 13 days of wash-out for lanreotide. Patients in Group B were treated with lanreotide for 30 days (Period 1) followed by octreotide for 30 days (Period 2) using the same drug doses used for Group A. Similarly, a wash-out period of at least 3 days was applied between the two treatment groups.

Clinical Assessment

Patients were assessed clinically at the beginning and end of each treatment period (on Day 1 and Day 30 for Periods 1 and 2). The following variables were recorded: 1) *quality of life*, which was based on the Index de Santé Perceptuel de Nottingham (ISPN), a French version of the Nottingham Health Profile[17,18] (this is a numerical system using a quality-of-life questionnaire that scores physical mobility, social isolation, pain, emotional reactions, energy, and sleep); 2) *clinical symptoms*, which were based on the frequency and severity of cutaneous flushes, diarrhea, abdominal pain, and wheeze (treatment efficacy was defined as a decrease $\geq$ 50% in the number of flushes and a frequency of $<$ 3 stools every 24 hours; and intensity of flushes and diarrhea were defined from an evaluation of the change in the appreciation of both symptoms recorded as absent, mild, moderate, or severe); and 3) *tumor markers*, which included plasma serotonin and urinary 5-hydroxyindoleacetic acid (5HIAA) levels. Quality-of-life questionnaires were completed by each patient prior to study visits, and an analysis was per-

formed by an independent expert who was blinded to the treatment groups. Levels of 5HIAA were analyzed using a centralized method to avoid interobserver differences. After completion of the study, patients were asked to state a preference for one of the two treatments and to provide reasons for their choice: This information was obtained by the investigating physician at each center. All adverse events were recorded.

Statistical Analysis

A comparison between the two treatment sequences for Group A and Group B was performed on quantitative variables using the Student *t* test, and variables outside of the normal distribution were compared using the Wilcoxon test. Qualitative variables were compared using the chi-square test or the Fischer exact test. Qualitative, ordered variables were analyzed using the Wilcoxon test. A difference was considered statistically significant when the *P* value of the two-sided test was < 0.05. An analysis also was performed on the efficacy and safety of treatment modalities: Quantitative variables were analyzed using an analysis of variance (Hill and Armitage method), and qualitative variables were assessed using the McNemar test.

Patient preferences for one of the two treatments were analyzed using the chi-square test, and qualitative, ordered variables were analyzed using a paired Wilcoxon test. A *P* value < 0.05 was considered statistically significant in the one-sided test.

TABLE 1
Demographic and Tumor Characteristics at Inclusion

Characteristic	% Group A (n = 16)	% Group B (n = 17)	% Total (n = 33)
Demographic characteristics			
Age (yrs)	63 ± 11.1	64 ± 10.8	63.5 ± 10.8
Sex			
M	50 (8)	47 (8)	48 (16)
F	50 (8)	53 (9)	52 (17)
History of tumor: Time from diagnosis (yrs)			
< 1	25 (4)	47 (8)	36 (12)
1–5	50 (8)	35 (6)	43 (14)
> 5	25 (4)	18 (3)	21 (7)
Previous SA treatment			
Octreotide	63 (10)	59 (10)	61 (20)
Lanreotide	13 (2)	0 (0)	6 (2)
Tumor site			
Primary tumor site			
Intestine	62.5 (10)	76 (13)	70 (23)
Pancreas	0 (0)	6 (1)	3 (1)
Other	37 (6)	18 (3)	27 (9)
Other localizations			
Lung/bronchi	(3)	(0)	(3)
Unknown	(3)	(0)	(3)
Stomach	(0)	(2)	(2)
Ovary	(0)	(1)	(1)
Metastases	100 (16)	100 (17)	100 (33)

SA: somatostatin analogues.
Numbers in parentheses denote actual patient numbers.

RESULTS

A total of 35 patients were recruited from 15 study centers, 33 of whom were randomized to either group. Two patients were excluded because they did not fulfill the inclusion criteria prior to randomization. Five patients withdrew from the study as a result of adverse events (n = 2 patients) or lack of efficacy (n = 3 patients). The two adverse events included 1 patient with bowel obstruction and 1 patient with pneumonia (the latter patient was thought to have tumor progression with pulmonary metastases). Therefore, 28 patients, 14 in each group, were evaluated in the efficacy analysis. All patients who received at least one injection of either somatostatin analogue were included in the safety analysis.

The characteristics of the patients in the two treatment groups were similar, and no significant differences were found with respect to age or gender (Table 1). The tumor characteristics at inclusion were comparable for both groups except for the presence of pulmonary localization in 3 patients in Group A and 2 patients with gastric localization in Group B (Table 1). Prior to inclusion in the trial, 89% of patients complained of flushes, 82% complained of diarrhea, 43% complained of abdominal pain, and only 7% complained of respiratory wheeze. No significant difference was found with respect to these symptoms in Groups A and B. Quality-of-life assessments, including physical mobility, social isolation, pain, emotional reactions, energy levels, and sleep, also were similar between the two groups prior to commencing treatment. When symptoms at the onset of each treatment period were analyzed, no difference was found in the intensity of flushes, the intensity of diarrhea, or the number of stools (Table 2). The mean number of flushes at the onset of Period 1 was 3.3 ± 2.4 flushes compared to 2.4 ± 1.8 flushes at the onset of Period 2 ($P = 0.05$) but did not vary with respect to treatment randomization. This implies that, except for the number of flushes, the wash-out period was effective in returning the patients to their baseline symptoms.

Change in Symptoms

The effects of treatment with either somatostatin analogue on the intensity of flushes and diarrhea are shown in Table 3. The disappearance of or improvement in the intensity of flushes was observed in 68% of patients (17 of 25) who received octreotide and in 54%

TABLE 2
Symptoms at the Onset of Each Treatment Schedule

Symptom	Onset period 1 (%)[a]	Onset period 2 (%)[a]	*P* value
Intensity of flushes (n = 28)			
Absent	3 (11)	2 (7)	
Mild	9 (32)	8 (29)	
Moderate	12 (43)	12 (43)	0.34
Severe	4 (14)	6 (21)	
Mean no. of flushes/day (n = 28)	3.3 ± 2.4	2.4 ± 1.8	0.05
Intensity of diarrhea (n = 28)			
Absent	5 (18)	7 (25)	
Mild	9 (32)	8 (28)	0.62
Moderate	10 (36)	10 (36)	
Severe	4 (14)	3 (11)	
Mean no. of stools/day (n = 28)	3.2 ± 1.7	2.8 ± 1.6	0.78

[a] Numbers given correspond to actual number of patients. Calculations were performed on patients who were symptomatic at the beginning of each period.

of patients (14 of 26) who received lanreotide. Diarrhea disappeared or improved in 50% of patients (11 of 22) who received octreotide and in 45% of patients (10 of 22) who received lanreotide. No significant differences were observed between the two somatostatin analogues with respect to intensity of flushes or diarrhea. The changes in the numbers of flushes and stool frequency are shown in Table 4. Patients experienced decreases in the number of flushes and the number of stools (by at least 50%) of 48% and 79%, respectively, when they received octreotide compared with 41% and 89%, respectively when they received lanreotide. One of the seven patients with abdominal pain had improved symptoms during the study period, and the symptoms of the single patient with bronchial wheeze remained unchanged. There was no significant difference between the two somatostatin analogue treatments with respect to the number of flushes or diarrhea.

Quality of Life

The changes in quality-of-life scores for patients who received octreotide compared with patients who received lanreotide, respectively (expressed as the mean difference ± standard deviation [SD]), were as follows: physical mobility, 1.2 ± 13.9 vs. 1.1 ± 12; social isolation, 1.6 ± 11.4 vs. 4.3 ± 18.9; pain, 4.5 ± 21.5 vs. 9.4 ± 25; emotional reaction, 2.6 ± 11.5 vs. 3.0 ± 21.5; energy, 7.8 ± 36.8 vs. 6.0 ± 28.6; and sleep, 3.3 ± 11.4 vs. −1.1 ± 20.8. There was no significant difference between the two treatment groups with regard to quality-of-life scores.

Biochemical Markers

The effect of treatment on biochemical tumor marker levels is shown in Table 5. The mean decrease in the 24-hour urinary 5HIAA level was ≈25% for both groups. A decrease ≥ 25% in the 24-hour 5HIAA level was observed in 50% of patients (12 of 24) who received octreotide and in 58% of patients (14 of 24) who received lanreotide. Plasma serotonin levels decreased by at least 25% in approximately one-third of the patients in both groups. These differences were not significantly different.

Adverse Events and Safety Analysis

Mild episodes of abdominal pain and or nausea and emesis were reported in 29% of patients while they were receiving octreotide and in 14% of patients while they were receiving lanreotide. Two patients (one in each treatment group) discontinued treatment prematurely due to tumor progression, which presented in one patient as pneumonia from pulmonary metastases and, in the other patient, as the development of ascites and progressive hepatic metastases, necessitating treatment with chemotherapy. Small bowel obstruction occurred in one patient and resolved with conservative treatment.

Patient Preference

When they were questioned about their preference of treatments, 68% of patients preferred lanreotide, and 32% preferred octreotide ($P = 0.03$). The reasons given by the 19 patients who preferred lanreotide were simplified mode of administration (n = 19 patients), improved quality of life (n = 16 patients), more efficacious in controlling symptoms (n = 11 patients), and fewer adverse effects (n = 4 patients). The 9 patients who preferred octreotide gave their reasons as more efficacious in controlling symptoms (n = 9 patients), improved quality of life (n = 6 patients), and fewer adverse effects (n = 5 patients). The preference of treatment did not vary significantly with respect to the order of administration (61% for Period 1 vs. 39% for Period 2; $P = 0.26$). No correlation was found between quality of life or patient preference with respect to previous treatment with somatostatin analogues using either lanreotide or octreotide.

DISCUSSION

This prospective study confirms previous reports that the long-acting somatostatin analogue lanreotide is effective in controlling symptomatic carcinoid syndrome and in lowering biochemical tumor markers.[15,16] Lanreotide and octreotide both were found to be capable of reducing episodes of flushing and diar-

TABLE 3
Change in Intensity of Flushes and Diarrhea[a]

	Octreotide[b]			Lanreotide[b]		
Symptom	Group A	Group B	Total	Group A	Group B	Total
Flushes (%)						
Disappearance	4 (16)	4 (16)	8 (32)	3 (12)	4 (15)	7 (27)
Improvement	6 (24)	3 (12)	9 (36)	4 (15)	3 (12)	7 (27)
Stabilization	2 (8)	4 (16)	6 (24)	4 (15)	5 (19)	9 (35)
Aggravation	0 (0)	2 (8)	2 (8)	2 (8)	1 (4)	3 (12)
Diarrhea (%)						
Disappearance	2 (8)	2 (8)	4 (16)	3 (12)	2 (8)	5 (19)
Improvement	5 (20)	2 (8)	7 (28)	3 (12)	2 (8)	5 (19)
Stabilization	4 (16)	6 (24)	10 (40)	3 (12)	8 (31)	11 (42)
Aggravation	0 (0)	1 (4)	1 (4)	1 (4)	0	1 (4)

[a] Numbers given correspond to actual numbers of patients. Intensity of flushes and diarrhea were defined from an evaluation of the change in the appreciation of both symptoms that were recorded as absent, mild, moderate, or severe (data not included here).
[b] Calculations were performed on patients who were symptomatic at the beginning of each period.

TABLE 4
Change in the Number of Flushes and Stools

	Octreotide (%)			Lanreotide (%)		
Symptom frequency	Group A	Group B	Total	Group A	Group B	Total
Decrease in frequency of flushes of least 50%	36	62	48	50	31	41
Decrease in frequency of stools of least 50%	86	71	79	100	79	89

TABLE 5
Urinary 5HIAA and Plasma Serotonin Levels Before and After Treatment

	Octreotide			Lanreotide		
Level	Group A	Group B	Total	Group A	Group B	Total
24 h urinary 5HIAA mg/24 hr (normal range ≤ 10 mg/24 hr) (n = 24)[a]						
At inclusion	57.4 ± 102.2	77.0 ± 59.5	81.8 ± 80.8	87.8 ± 105.0	94.3 ± 124.9	91.4 ± 113.7
Mean decrease	32.3 ± 82.1	14.3 ± 36.5	22.5 ± 60.9	21.5 ± 94.9	29.1 ± 123.5	25.6 ± 109.0
Plasma serotonin levels μmol/L (normal range 0.1–0.9 μmol/L) (n = 22)[a]						
At inclusion	2.85 ± 2.03	3.52 ± 1.41	3.21 ± 1.71	3.44 ± 2.03	3.98 ± 1.02	3.74 ± 1.54
Mean decrease	0.05 ± 1.73	0.49 ± 0.84	0.29 ± 1.31	0.63 ± 0.90	0.24 ± 1.16	0.42 ± 1.04

[a] Urinary 5HIAA levels were not available for 4 patients due to incomplete collection, and plasma serotonin levels were not available for 5 patients. These patients were excluded from the tumor cell marker analysis.

rhea in a well-matched group of patients. Somatostatin and its analogues have not been shown definitively to produce objective results on carcinoid tumor regression[14–16,19–21]; however, their efficacy in controlling the debilitating symptoms associated with carcinoid syndrome makes them invaluable for a large proportion of patients who suffer from this disease. This first direct crossover comparison between patients who underwent these treatments shows that lanreotide and octreotide are equally effective in reducing both the number and intensity of flushes and diarrhea. The intensity of flushes was found to decrease in >50% of patients who received either treatment, whereas octreotide appeared to be slightly more efficacious than lanreotide (68% vs. 54%, respectively), although the difference was not significant. The reduction in stool frequency was impressive in patients who received either form of treatment (89% for lanreotide vs. 79% for octreotide). The reappearance of symptoms after the wash-out period indicates that

both drugs were cleared effectively from the system at the end of Period 1, thus limiting the possibility of carryover effects from treatment from treatment Period 1 to Period 2, although the lack of plasma levels prevents the definitive conclusion that carryover effects did not occur. The clinical impact on carcinoid-induced bronchial wheeze could not be evaluated from this study, because only one patient had this symptom at the time of enrollment.

We previously demonstrated that, in the treatment of patients with carcinoid syndrome, lanreotide is effective for as long as up to 6 months of therapy.[16] The ideal form of therapy in the symptomatic treatment of patients with advanced malignant diseases should be both efficacious and also acceptable to patients in terms of ease of administration and with an acceptably low risk of adverse effects. In this regard, a direct comparison between lanreotide and octreotide with an assessment of quality-of-life scores and patient preference was evaluated. Although no differences in quality-of-life scores were observed between those who received octreotide and those who received lanreotide, patients significantly preferred lanreotide over octreotide largely due to the simplified mode of administration ($P = 0.03$). Improved quality of life was stated as a reason for preferring lanreotide in 16 patients (57%) compared with only 6 patients (21%) who preferred octreotide. Despite an obvious preference for lanreotide, an objective difference in terms of improved quality of life, as assessed by quality-of-life questionnaires, was not observed between the two forms of somatostatin analogue treatment. Possible explanations for this may be the lack of sensitivity of the ISPN scoring system in reflecting a simplified form of drug administration. Such difficulties with quality-of-life scores have been outlined previously.[22,23] An evaluation of quality-of-life scores over an extended time, perhaps up to 6 months, or the use of a more sensitive scoring analysis may show a significant difference between the two drugs.

In accordance with previous data, treatments with both somatostatin analogues were remarkably well tolerated.[16,24] The poor effect of lanreotide and octreotide in controlling abdominal pain, which is not infrequent in patients with gastrointestinal carcinoids, is not surprising, because the etiology of abdominal pain is believed to arise from mesenteric fibrosis that is induced locally from the tumor and not from its secreted, circulating peptides.[25] Whether these somatostatin analogues further augment abdominal pain by decreasing intestinal mobility in unknown. One case of small bowel obstruction occurred during the study period when the patient was receiving lanreotide. This event has been reported previously in patients who received both lanreotide and octreotide for the treatment of intestinal carcinoids.[16,26] Patients with gastrointestinal carcinoid tumors have an increased risk for this complication, which also is believed to arise from fibrosis of the mesentery and adjacent structures and is unlikely to be a direct effect of these medications.[25] Only one patient complained of pain at the injection site that occurred when the patient was receiving lanreotide, and no patient developed gallstones or steatorrhea, which are known complications of somatostatin analogs.[16,27] The absence of cholelithiasis and steatorrhea may be secondary to the relatively short treatment period. However, neither abdominal ultrasound nor fecal fat measurements were performed as part of the analysis.

In summary, this crossover study comparing the efficacy of octreotide and lanreotide in the treatment of patients with symptomatic carcinoid tumors showed that both were well tolerated and equally effective in terms of symptomatic control and reduction of tumor marker levels. Although there was no significant difference in terms of quality-of-life scores, lanreotide was preferred by most patients largely due to its simplified mode of administration and subjective improvement in quality of life.

REFERENCES

1. Godwin JD II. Carcinoid tumors. An analysis of 2,837 cases. *Cancer* 1975;36:560–9.
2. Moertel CG. Karnofsky memorial lecture. An odyssey in the land of small tumors. *J Clin Oncol* 1987;5:1502–22.
3. Ahlman H, Westberg G, Wangberg B, Nilsson O, Tylen U, Schersten T, et al. Treatment of liver metastases of carcinoid tumors. *World J Surg* 1996;20:196–202.
4. Foster JH, Berman MM. Solid liver tumors. *Major Probl Surg* 1977;22:1–342.
5. Chuang VP, Wallace S. Hepatic artery embolization in the treatment of hepatic neoplasms. *Radiology* 1981;140:51–8.
6. Moertel CG, Johnson CM, McKusick MA, Martin JK Jr., Nagorney DM, Kvols LK, et al. The management of patients with advanced carcinoid tumors and islet cell carcinomas. *Ann Intern Med* 1994;120:302–9.
7. Venook AP. Embolization and chemoembolization therapy for neuroendocrine tumors. *Curr Opin Oncol* 1999;11:38–41.
8. Kvols LK, Buck M. Chemotherapy of metastatic carcinoid and islet cell tumors. A review. *Am J Med* 1987;82:77–83.
9. Tiensuu Janson EM, Oberg KE. Carcinoid tumors. *Baillieres Clin Gastroenterol* 1996;10:589–601.
10. Oberg K, Norheim I, Theodorsson E. Treatment of malignant midgut carcinoid tumors with a long-acting somatostatin analogue octreotide. *Acta Oncol* 1991;30:503–7.
11. Oberg K. Neuroendocrine gastrointestinal tumors. *Ann Oncol* 1996;7:453–63.
12. Arnold R. Medical treatment of metastasizing carcinoid tumors. *World J Surg* 1996;20:203–7.
13. Kvols LK. Therapy of the malignant carcinoid syndrome. *Endocrinol Metab Clin North Am* 1989;18:557–68.

14. Arnold R, Trautmann ME, Creutzfeldt W, Benning R, Benning M, Neuhaus C, et al. Somatostatin analogue octreotide and inhibition of tumor growth in metastatic endocrine gastroenteropancreatic tumors. *Gut* 1996;38:430–8.
15. Scherubl H, Wiedenmann B, Riecken EO, Thomas F, Böhme E, Räth U. Treatment of the carcinoid syndrome with a depot formulation of the somatostatin analogue lanreotide. *Eur J Cancer* 1994;30A:1590–1.
16. Ruszniewski P, Ducreux M, Chayvialle JA, Blumberg J, Cloarec D, Michel H, et al. Treatment of the carcinoid syndrome with the long-acting somatostatin analogue lanreotide: a prospective study in 39 patients. *Gut* 1996;39(2): 279–83.
17. Bucquet D, Condon S, Ritchie K. The French version of the Nottingham Health profile. A comparison of weights with those of the source version. *Soc Sci Med* 1990;30:829–35.
18. McEwen J. The Nottingham Health Profile in quality of life. In: Walker SR, Rosser, RM, editors. Assessment and application. Oxford, United Kingdom: MTP Press, 1988:95–111.
19. Janson ET, Oberg K. Long-term management of the carcinoid syndrome. Treatment with octreotide alone and in combination with alpha-interferon. *Acta Oncol* 1993;32:225–9.
20. Souquet JC, Sassolas G, Forichon J, Champetier P, Partensky C, Chayvialle JA. Clinical and hormonal effects of a long-acting somatostatin analogue in pancreatic endocrine tumors and in carcinoid syndrome. *Cancer* 1987;59:1654–60.
21. Trautmann ME, Neuhaus C, Lenze H, Benning R, Benning M, Dennler HJ, et al. The role of somatostatin analogs in the treatment of endocrine gastrointestinal tumors. *Horm Metab Res* 1993;27(Suppl):24–7.
22. Pouchot J, Guillemin F, Coste J, Bregeon C, Sany J. Validation of the French version of the arthritis impact measurement scales 2 and comparison with the French version of the Nottingham Health Profile. "Quality of Life in Rheumatology" task force. *Rev Rhumatol* 1999;63:389–404.
23. Fitzpatrick R, Fletcher A, Gore S, Jones D, Spiegelhalter D, Cox D. Quality of life measures in health care. I. Applications and issues assessment. *BMJ* 1992;305:1074–7.
24. Scarpignato C. Somatostatin analogues in the management of endocrine tumors of the pancreas. In: Mingon M, Jensen RT, editors. Endocrine tumors of the pancreas. Frontiers in gastrointestinal research. vol. 23. Basel: Karger, 1995:385–414.
25. Kvols LK. Gastrointestinal carcinoid tumors and the management of the carcinoid syndrome. In: Feldmen M, Scherschlidt BF, Sleisenger MH, editors. Gastrointestinal and liver disease. ed 6. 1998;110:1831–1843.
26. Chayvialle JA. Sandostatin and carcinoid tumors in France: experience in the Lyon area. *Digestion* 1990;45(Suppl 1): 23–6.
27. Arnold R, Frank M. Gastrointestinal endocrine tumors: medical management. *Baillieres Clin Gastroenterol* 1996;10:737–59.