Somatostatin analogs: is one better than other?

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Two important studies have recently demonstrated a significant efficacy of somatostatin analogs (SSas) in neuroendocrine tumors (NETs) and since then, an interesting debate on which of the two drugs could be considered more effective has developed within the scientific community.[1–4]

Octreotide and lanreotide constitute the standard of care for the medical treatment of NETs. They have a highly improved stability compared with natural somatostatin, allowing for long-term treatment. They have a restricted somatostatin receptor (sst) affinity profile, with high sst2 affinity, lower sst3 (higher for octreotide *versus* lanreotide) and sst5 affinity and no sst1 or sst4 affinity.[5]

In the PROMID trial, treatment-naïve patients with histologically confirmed locally unresectable or metastasized, well-differentiated (95.3%) or moderately differentiated (4.7%), positive Octreoscan® (74.1%), with functioning and nonfunctioning NETs of midgut or unknown origin, were randomized to receive either monthly octreotide LAR® 30 mg or placebo. Data were reported on 85 patients (43 octreotide LAR; 42 placebo). Median time to progression (mTTP) in the octreotide LAR® and placebo groups was 14.3 months and 6 months, respectively [hazard ratio (HR) = 0.33; 95% confidence interval (CI) = 0.20–0.57; $p = 0.000037$]. The study did not finish its intended accrual due to the lack of efficacy in the placebo arm.[1]

Conversely, CLARINET [Lanreotide® antiproliferative response in patients with gastro-entero-pancreatic (GEP)-NET], a large prospective phase III, randomized, double-blind, placebo-controlled, multicenter trial, evaluated the antiproliferative effect of Lanreotide® in patients with well- or moderately differentiated (defined as having Ki67 <10%) nonfunctioning GEP-NETs.[2] The study finished its accrual and it enrolled 204 patients, including pancreatic tumors (45% of all enrolled patients). All patients had not previously received SSas, interferon, chemoembolization or chemotherapy within 6 months prior to study entry.

The patients were randomized to receive either 120 mg Lanreotide® Autogel® ($n = 101$) or placebo ($n = 103$) and at a timepoint of 2 years following initiation of treatment, median progression-free survival (PFS) was not reached with Lanreotide® compared with 18 months obtained with placebo ($p = 0.0002$). Neither disease progression nor death occurred in 62% of Lanreotide® patients compared with 22% of placebo patients.

Table 1 summarizes the major differences between the two trials. Among them, one of the interesting differences is that in the PROMID study placebo arm the TTP was only about 6 months, whilst in the CLARINET trial, the PFS, which is somewhat similar, is far longer, at 18 months. This may suggest that in the CLARINET study, patients with more indolent disease were selected and this reflects the differences in the eligibility criteria. Another relevant difference is the median time since diagnosis, which was 4.3 months in PROMID and 33 months in CLARINET, thus suggesting that in the latter study, median time since M1 diagnosis could have been considered.

Nevertheless, despite these differences, in both of the studies the results in the treatment and the placebo arms were highly significantly different, confirming the antiproliferative effect of SSas. Therefore, in the clinical setting, the rationale for their use is not only limited to hormonal symptom control, but also against tumor cell proliferation. Thus, the indication widened to both functioning and nonfunctioning GEP-NETs.

Table 1. Major differences between PROMID and CLARINET trials.

	PROMID study	CLARINET study
SSa dose	Octreotide LAR 30 mg	Lanreotide® AG 120 mg
Number of patients	85	204
Primary endpoint	Time to progression	Progression-free survival
Primary tumor	Midgut or unknown	GEP or unknown
Grading	G1 (Ki67 <2% in 95% of patients)	G1 + G2 (Ki67 <2% in 68% of patients and <10% in 32% of patients)
Liver involvement	⩽10% in 75% of patients	⩽10% in 49% of patients >25% in 39% of patients
Syndrome	39% of patients	Nonfunctioning (exclusion criterion)
Prior therapies	No	Yes
Median time since diagnosis	4.3 months	33 months
Response assessment	WHO	RECIST
Median PFS SSa arm	14.3 months (p = 0.000072)	NR (p = 0.0002)
Median PFS placebo arm	6 months	18 months
Hazard ratio	0.34 (95% CI 0.20–0.59)	0.47 (95% CI 0.30–0.73)
Overall survival	Not significant	Not significant

GEP, gastro-entero-pancreatic tumors; SSa, somatostatin analogs; PFS, progression-free survival; WHO, World Health Organization; RECIST, response evaluation criteria in solid tumors; CI, confidence interval; NR, not reported.

Moreover SSas, according to the CLARINET and PROMID trial results, represent an efficacious treatment option in functioning and nonfunctioning locally advanced or metastatic G1 and G2 GEP-NETs, also in patients without a prior observation period of spontaneous tumor growth.[6–8]

However, their approval for clinical use is quite different. In fact, Lanreotide® was approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with unresectable, well- or moderately differentiated, locally advanced or metastatic GEP-NETs, whichever the function. The recommended dose and schedule for Lanreotide® for GEP-NET is 120 mg administered by deep subcutaneous injection every 28 days, to be continued until disease progression or unacceptable toxicity.

Octreotide LAR® was approved by the FDA only for the treatment of patients with symptoms associated with functional GEP-NETs and of patients with advanced NETs of the midgut or of unknown primary origin. It should be continued in the absence of tumor progression.

The recommended dose is 30 mg intramuscularly, every 4 weeks.

According to GoodRx in the USA, the cost of a 30 mg vial is between $5441 and $5706, whilst the cost of Lanreotide® (120 mg vial) ranges from $6631 to $7147,[9] but final costs are rather heterogeneous and vary greatly between institutions.

On the basis of all the aforementioned considerations, despite the difficulties in performing cross-trial comparisons, the answer to the question whether one SSa is better than the other should be 'maybe', at least according to different approved indications by the same regulatory authority. Is it really true or just a result of the different timing of the studies? This question remains unsolved on clinical grounds.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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