Note

An Open, Phase III Study of Lanreotide (Somatuline PR®) in the Treatment of Acromegaly

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Abstract. Acromegaly is a disorder caused by excessive secretion of human growth hormone (GH). Somatostatin and its analogue—prolonged release formulation, lanreotide (Somatuline PR), inhibit the secretion of growth hormone. The aim of this open Phase III study was to investigate the clinical efficacy of lanreotide in the treatment of six acromegalic patients with a mean age of 44 ± 13 yr including two patients with diabetes mellitus. All the patients previously received transsphenoidal or transcranial hypophysectomy. Lanreotide was given intramuscularly every 2 weeks at a fixed dose of 30 mg for 12 weeks. Serum GH and insulin-like growth factor-I (IGF-I) levels were evaluated before, 2, 6 and 12 weeks after treatment. After 12 weeks of treatment, mean (± SEM) GH levels decreased from 24.8 ± 12.5 to 6.9 ± 3.3 ng/ml and mean serum IGF-I levels decreased from 689 ± 282 to 430 ± 216 ng/ml. Abdominal ultrasonographic examinations showed no gallbladder stone or bile sand formation before or after the treatment. Three of the patients who did not receive octreotide presented with manifestations of mild gastrointestinal adverse effect such as mild abdominal pain and diarrhea. In conclusion, lanreotide is effective in the treatment of active postoperative acromegaly.

Key words: GH, Insulin-like growth factor-I, Bromocriptine, Somatostatin

ACROMEGALY is a disorder caused by the excessive production of human GH. Recent advances in the diagnosis and management of acromegaly have allowed patients to be treated earlier, more effectively, and with fewer side effects. The increased mortality rate of active acromegaly patients is well known [1–3]. Previously diabetic and cardiovascular complications of acromegaly have resulted in a doubling of the expected mortality rate [4]. This and the considerable morbidity associated with acromegaly, has driven the search for more effective management of patients who are unsuitable for surgery, or who require treatment while waiting for radiotherapy. The GH levels of 19% of acromegalic patients can be controlled to the normal range with bromocriptine [5], but the remainder of the patients are either unable to tolerate bromocriptine or are resistant to it. Because somatostatin and its synthetic analogues inhibit the secretion of GH [6–9], for patients who are resistant to other forms of therapy, the advent of the long acting analogues of somatostatin has provided a viable alternative [10, 11]. The aim of the study was to investigate the ability of the prolonged release formulation of somatostatin (lanreotide) to control GH and insulin-like growth factor-I (IGF-I) levels in patients with acromegaly and to examine the adverse effects of lanreotide during treatment.
Subjects and Methods

The patients fulfilled certain criteria prior to entry into this study. They exhibited signs of active acromegaly, which was defined as random serum GH of more than 5 ng/ml and failure to suppress serum GH to within 2 ng/ml in an oral glucose tolerance test (OGTT). Subjects with any of the following would render him or her ineligible for inclusion: age less than 18 yr; women of child bearing age not using an effective contraceptive method; pregnancy; overt hepatic, renal or cardiac disease; gall bladder disease or gall stones; known hypersensitivity to any of the test materials or related compounds; unwillingness or inability to fully comply with the protocol; participation in any other clinical study within 30 days of the start of this study; and not living in the country where the investigators' hospital is situated. Patients receiving other somatostatin therapies ceased their therapy at least 7 days prior to this study. Patients receiving dopamine agonist therapy quit their therapy one month prior to the initial hormone assessment. The study was approved by the ethical committee of Chang Gung Medical Center; and all the patients gave written informed consent before entry into the study.

All the patients previously received transsphenoidal hypophysectomy and one of them received a secondary transcranial hypophysectomy. None of the patients received external radiotherapy. Persistently high serum GH and IGF-I levels were observed in the patients after the surgery. All the patients received intramuscular injections of 30 mg lanreotide (Somatuline PR®) every 2 weeks for 12 weeks. All had an assessment of clinical, pituitary and hormonal parameters before and 3 months after treatment with lanreotide. Serum GH and IGF-I levels were reassessed at 2, 6 and 12 weeks after treatment. The minimum detectable quantities of serum GH and IGF-I were 0.1 ng/ml and 8 ng/ml, respectively. The intro/inter assay variations in serum GH levels are 5.13–6.53% and 5.07–7.64% (CV%) and the intro/inter assay variations in serum IGF-I levels are 3.26–8.28% and 3.33–8.97% (CV%).

Lanreotide (Somatuline PR®) was obtained from Beaufour-Ipsen International of France. Lanreotide is a cyclic octapeptide characterized by the presence of the ring of D-β NaI (which enhances its selectivity) (Fig. 1). Lanreotide and octreotide are both analogues of somatostatin, but are not the same compounds. The active principle lanreotide was enclosed in microspheres. Somatuline PR® contained 30 mg of lanreotide per vial.

Clinical examinations were conducted: blood pressure, pulse, weight and height, blood cells counts, biochemistry tests including serum Na, K, Ca, P, creatinine, BUN, A/G, ALT and/or AST, bilirubin, blood sugar and GH. Oral glucose tolerance and abdominal ultrasonographies were performed before and 12 weeks after treatment. Hematology and biochemistry studies were performed at 2, 6 and 12 weeks. Forms were given to the patients to record daily symptoms, blood sugar twice per week (monitored with a portable glucometer), and the date of the next appointment. All adverse events, regardless of severity or relatedness to the study drug were recorded on the adverse event forms.

Clinical characteristics of the six patients with acromegaly enrolled in this study are shown in Table 1. Of the six patients, three were male and three were female with a mean age of 44 ± 13 years (range 27–59 years old). Two of these patients were diagnosed as having diabetes mellitus (DM) before treatment. One received insulin therapy, and the other was treated with diet only. Five of the patients received bromocriptine therapy before the study and two patients received octreotide treatment. All the patients completed lanreotide treatment for 12 weeks.

Results

Table 2 shows serum GH and IGF-I levels in six patients during the treatment with lanreotide. After
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12 weeks of treatment, the mean GH level decreased from $24.8 \pm 12.5$ to $6.9 \pm 3.3$ ng/ml. All the patients except patient 5 had lower GH levels at 2 weeks after beginning the treatment. The GH level was higher at the second week and lowered thereafter. Table 2 shows IGF-I levels of six patients before and after treatment with lanreotide. After treatment, mean IGF-I levels decreased from $689 \pm 282$ to $430 \pm 216$ ng/ml, but IGF-I levels were higher in two patients (patients 1 and 2). Decreases of less than 25% were found in patients 2 and 5. In this study, the response of the GH levels (mean,
70% decrease) was more prominent than the response of IGF-I levels (mean, 38% decrease). The ranges of decrease in GH and IGF-I are 44 to 97% and 10 to 84%, respectively.

Clinical examination results including blood pressure, pulse, weight and height, hematology, biochemistry and oral GTT of the six patients revealed no significant difference and after the treatment (Fig. 2). Abdominal ultrasonographic examinations showed no gallbladder stone or bile sand formation during the study period. Three patients (patients 1, 5 and 6) who did not previously receive octreotide treatment had a mild adverse gastrointestinal effect which manifested as mild abdominal pain and diarrhea. The adverse effects subsided after treatment with anti-diarrhea medication (kaolint-pectin suspension).

**Discussion**

Until recently, the only available agent for acromegaly, octreotide was given either as a continuous infusion or in three daily doses subcutaneously [12–14]. The mode of administration of octreotide and its cost are limiting factors in its use, but recently an alternative to octreotide, lanreotide (Somatuline PR®), has become available [9,15]. Of the six patients in this study, two received octreotide treatment before the study including one patient with diabetes mellitus. Minor side effects such as diarrhea or loose stool passage were experienced by the patients who had no previous treatment with octreotide. Since only two patients previously received octreotide treatment, it is difficult to compare the two kinds of treatment, but a recent study showed that intramuscular injection of lanreotide was as effective as continuous subcutaneous infusion of octreotide in the control of GH hypersecretion [9].

Lanreotide, a long acting analogue of somatostatin, binds preferentially to pituitary somatostatin receptors [16], to inhibit GH secretion in healthy men [17]. Lanreotide has an increased potency for growth hormone inhibition and a prolonged plasma half life compared with the
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parent compound. An antiproliferative effect of lanreotide has been shown in vitro on several tumour cell lines. Lanreotide completely inhibited cell proliferation of cultured pancreatic carcinoma cells, breast carcinoma cells and small cell lung carcinoma cells [18]. After subcutaneous injection of octreotide in a non-prolonged release formulation, the peak plasma concentration was at 30 min. The plasma elimination half-life is 1.2 h. Although a fixed dose of lanreotide was used in our study, serum GH responded well to the treatment in most patients. Only one patient had a transiently increased GH level during the second week after treatment. Long-term effects of lanreotide confirmed the efficacy and the tolerance of 30 mg intramuscularly every 10–14 days to control acromegaly [19, 20].

Somatostatin is known to suppress the mitotic effect of growth factors such as epidermal growth factor (EGF) and IGF-I [21]. Growth hormone stimulates cellular differentiation directly and through local production of growth factors [22]. Insulin-like growth factor (IGF), platelet-derived factor (PDGF), fibroblast growth factor (FGF), transforming growth factor (TGF), bombesin and probably others are intricately involved in the proliferation of normal, benign and malignant cells [22–24]. Somatostatin has inhibitory effects on these growth factors and in some cases reduces the levels, either by a direct effect or through the reduction of GH [25, 26]. The IGF-I response of patients to lanreotide in our study varied. Unlike GH, 50% of the decrease in IGF-I after lanreotide treatment occurred in only one patient. This phenomenon might be partly due to the still relatively high GH levels after injection, even though GH levels become lower as compared to untreated values. More frequent injections might be effective in normalizing both serum GH and IGF-I levels. Further study will be required to prove this. Our study on the responses of GH and IGF-I after lanreotide treatment is similar to the results of AJ-Maskari et al. [15] and Marek et al. [20]. These finding of a weaker response of IGF-I than GH after treatment are similar to the results after octreotide treatment [27, 28]. Long-term lanreotide treatment with a short period of injections could allow normalization of IGF-I in 63.6% of the patients [19, 29].

In conclusion, in our study lanreotide was effective in the treatment of active acromegaly. No obvious adverse effects were noted. Paradoxical responses of IGF-I during this short period of treatment need further investigation.

References

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