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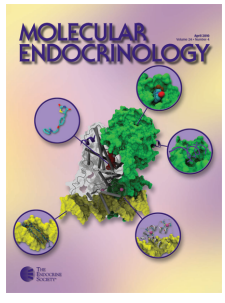

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Efficacy of the New Long-Acting Formulation of Lanreotide (Lanreotide Autogel) in the Management of Acromegaly

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Lanreotide Autogel is a new long-acting aqueous preparation of lanreotide for the treatment of acromegaly and is administered by deep sc injection from a small volume, prefilled syringe. The aim of this study was to evaluate the efficacy and safety of this new long-acting formulation in a large population of acromegalic patients previously responsive to lanreotide 30 mg, im (sustained release microparticle formulation). Lanreotide Autogel was administered by deep sc injection every 28 d to 107 patients (54 males and 53 females; mean age, 54 ± 1.2 yr). All patients had been treated with lanreotide (30 mg) for at least 3 months before study entry and had a mean GH level less than 10 ng/ml after at least 4 subsequent im injections every 14 d (48%), 10 d (32%), or 7 d (20%). Treatment was switched from lanreotide 30 mg injected every 14, 10, or 7 d to 60, 90, or 120 mg lanreotide Autogel, respectively, every 28 d. After three fixed dose injections of lanreotide Autogel, mean lanreotide levels were similar to those obtained at steady state with lanreotide 30 mg. During lanreotide Autogel treatment, the control of acromegalic symptoms was comparable with that previously achieved during lanreotide 30 mg treatment. After 3 injections of lanreotide Autogel, mean GH (2.87 ± 0.22 ng/ml) and IGF-I (317 ± 15 ng/ml) values were comparable with those recorded at the end of lanreotide 30 mg treatment (GH, 2.82 ± 0.19 ng/ml; IGF-I, 323 ± 16 ng/ml). GH levels below 2.5 ng/ml and age-/sex-normalized IGF-I were achieved in 33% and 39% of patients during lanreotide 30 mg and lanreotide Autogel treatment, respectively. Diarrhea, abdominal pain, and nausea were reported by 38%, 22%, and 18% of patients during lanreotide 30 mg treatment and by 29%, 17%, and 9% of patients, respectively, during lanreotide Autogel treatment. In conclusion, this clinical study shows that lanreotide Autogel is at least as efficacious and well tolerated as lanreotide 30 mg. This new long-acting lanreotide formulation, lanreotide Autogel, which is administered from a small volume, prefilled syringe by deep sc injection, is therefore likely to improve the acceptability of medical treatment for patients requiring long-term somatostatin analog therapy. (*J Clin Endocrinol Metab* 87: 99–104, 2002)

TREATMENT WITH somatostatin analogs, such as lanreotide and octreotide, is the first-line medical therapy for acromegaly (1–3). The suppressive effects of these analogs on somatotroph activity are reversible and do not persist for long after drug withdrawal. Long-acting release forms of somatostatin analogs, such as lanreotide 30 mg and octreotide-LAR, avoid the drawback of daily sc injections or continuous infusion using a pump. These depot formulations have been produced by the incorporation of lanreotide or octreotide in microparticles of biodegradable polymer and are injected im every 7–28 d. In short-term (4–6) and long-term (7, 8) clinical studies, lanreotide 30 mg achieves a control of GH hypersecretion similar to that previously obtained with daily sc injections or continuous infusion of octreotide. However, long-term treatment of acromegaly with fewer injections should further improve patient acceptability of this therapy.

Lanreotide Autogel is a new delivery formulation (manufactured by Beaufour-Ipsen Group, Paris, France), which is available in a small volume, prefilled syringe and is administered by deep sc injection. The aim of this study was to evaluate the efficacy and safety of this new long-acting lanreotide preparation in acromegalic patients previously responsive to lanreotide 30 mg.

Abbreviations: CI, Confidence interval.

Subjects and Methods

Patients

A total of 144 acromegalic patients (69 males and 75 females), aged 53 ± 1 yr (mean ± SEM), were included in this open comparative multicenter study (Intend to Treat population), after having been assessed for the safety analysis. Hypertension, diabetes mellitus, and impaired glucose tolerance were present in 38%, 26%, and 12% of the patients, respectively. Thirty-five percent of them had received hormonal replacement therapy for partial or complete hypopituitarism. Before somatostatin analog therapy, the mean IGF-I level was 646 ± 27 ng/ml. During lanreotide 30 mg administration, 11 patients withdrew due to adverse events unrelated to lanreotide or to protocol deviations (pancreatic neoplasm, n = 1; lung cancer, n = 1; protocol deviation, n = 3; mean GH >10 ng/ml at the end of treatment, n = 6). A total of 26 patients also withdrew during lanreotide Autogel administration due to

adverse events (hot flushes, mild nausea, and tenesmus, n = 1) and protocol deviation (n = 25). Overall, 107 patients (54 males and 53 females; mean age, 54 ± 1.2 yr) completed the study in accordance with the protocol (*i.e.* Per Protocol population).

The mean time since diagnosis of acromegaly was 11 ± 0.8 yr (mean ± SEM). A total of 83 patients had undergone pituitary surgery, and 49 had received external radiotherapy at least 6 months and 1 yr, respectively, before the study. These patients had a diagnosis of active acromegaly (basal mean GH level >5 ng/ml, elevated age-normalized IGF-I, or GH level >2 ng/ml after an oral glucose tolerance test) after surgery and/or radiotherapy and within 5 yr before the study. The mean residual tumor size was 16 ± 1 mm (n = 60). All patients had been treated with im injections of lanreotide 30 mg for at least 3 months before study entry and were considered to be responsive to the somatostatin analog lanreotide because they had a mean plasma GH level less than 10 ng/ml during lanreotide 30 mg administration. None of the patients received either a dopamine agonist or another somatostatin analog treatment during the study. All patients gave written informed consent, and the study was approved by the institutional ethics committee of each study center.

Study protocol

During the first part of the study, lanreotide 30 mg was administered every 14, 10, or 7 d to 48%, 32%, or 20% of the patients, respectively. Each patient received five im injections. When the next injection was due, patients were injected with lanreotide Autogel administered via a prefilled syringe. Patients received 60, 90, or 120 mg by deep sc injection every 28 d instead of lanreotide 30 mg by im injection every 14, 10, or 7 d, respectively. Three 28-d fixed dose injections were administered. Immediately before im or deep sc injection and after overnight fasting, blood was taken every 30 min for 4 h to provide nine measurements of GH concentration. Plasma IGF-I and lanreotide levels were also determined immediately before lanreotide 30 mg and lanreotide Autogel injections.

To evaluate the clinical efficacy of lanreotide, patients were asked to grade each of their symptoms (headache, night sweats, asthenia, swelling of extremities, and joint pain) as absent, mild, moderate, or severe at the end of each treatment period. To assess adverse events, gastrointestinal symptoms (diarrhea, abdominal pain, nausea, constipation, and vomiting) and symptoms local to the injection site (pain, itching, induration, and redness) were documented at each visit before and 30 min after each lanreotide injection.

Blood samples for hematology and biochemistry analyses were taken, and gallbladder echography was performed at the end of lanreotide 30 mg and lanreotide Autogel treatments.

Hormone assays

The plasma GH concentration was measured using an immunoradiometric assay from Nichols Institute Diagnostics (San Juan Capistrano, CA), with a detection limit of 0.02 ng/ml and intra- and interassay coefficients of variation of less than 4.2% and 7.2%, respectively. After an ethanol-acid extraction, a plasma IGF-I assay was performed by means of the IGF-I immunoradiometric assay kit from Nichols Institute Diagnostics. The detection limit of this assay was 6 ng/ml, and the intra- and interassay coefficients of variation were less than 3.3% and 10.3%, respectively. The concentration of lanreotide was analyzed by an RIA method with a detection limit of 0.08 ng/ml, and intra- and interassay coefficients of variation of less than 5% and 13%, respectively. All hormone and lanreotide assays were centralized.

Data analysis

A sample size of 100 patients in the Per Protocol population provides a power of greater than 80% to demonstrate the noninferiority of lanreotide Autogel. This noninferiority study was designed to show that lanreotide Autogel was not less effective than lanreotide 30 mg in controlling acromegaly as measured by mean GH levels. GH and IGF-I levels were analyzed using ANOVA, and lanreotide Autogel was considered noninferior to lanreotide 30 mg if the upper limit of the 95% confidence interval (CI) did not exceed 1.25. This approach is similar to that recommended to test noninferiority of pharmacokinetic parameters. The primary population was the Per Protocol one; however, to show the robustness of the results, the analysis was also performed on the Intend to Treat population. Subgroup analyses were also performed according to the dose of lanreotide Autogel received (60, 90, and 120 mg). Descriptive statistics for lanreotide serum levels were presented for main time points.

Results

Efficacy of lanreotide Autogel injections

The mean plasma GH level was 2.82 ± 0.19 ng/ml (mean ± SEM) 7–14 d after the last lanreotide 30 mg injection, and this increased to 3.51 ± 0.28 ng/ml at d 28 after the first injection of lanreotide Autogel when the serum lanreotide concentration was at the nadir, confirming that patients had active GH-secreting pituitary tumors. After the three lanreotide Autogel injections, the mean GH value decreased to 2.87 ± 0.22 ng/ml and was comparable with the value recorded at the end of lanreotide 30 mg treatment (upper 95% CI, 1.041; this value is lower than the 1.25 limit, demonstrating that lanreotide Autogel is no less effective than lanreotide 30 mg; Fig. 1A and Table 1). The results in the Intend to Treat population show a similar trend (upper 95% CI, 1.078). The changes in the GH value were similar for each dose group of patients, and mean GH levels were lower in the 60 mg group (2.33 ± 0.25 ng/ml) and higher in the 120 mg group (3.92 ± 0.48 ng/ml) than in the 90 mg group (3.03 ± 0.45 ng/ml) after the three lanreotide Autogel injections.

The mean plasma IGF-I value measured during lanreotide 30 mg treatment (323 ± 16 ng/ml) also confirmed noninferiority after one (345 ± 16 ng/ml) or three (317 ± 15 ng/ml) injections of lanreotide Autogel (upper 95% CI, 1.034 in the Per Protocol population, and 1.022 in the Intend to Treat population; Fig. 1B).

During lanreotide 30 mg treatment, mean GH levels less than 2.5 ng/ml and serum age-normalized IGF-I values were present in 51 (48%) and 48 (45%) patients, respectively. After the 3 lanreotide Autogel injections, the number of patients with GH levels less than 2.5 ng/ml and the number of patients with age-normalized IGF-I values were 60 (56%) and 51 (48%), respectively. The numbers of patients with both GH below 2.5 ng/ml and age-normalized IGF-I levels were 35 (33%) and 42 (39%) at the end of lanreotide 30 mg and lanreotide Autogel treatments, respectively.

During lanreotide 30 mg treatment, most patients reported acromegalic symptoms that were mild or moderate in severity. The control of clinical symptoms of acromegaly during lanreotide Autogel treatment was comparable with that previously achieved during lanreotide 30 mg injections. The most common symptom was joint pain, reported by 39% of patients during lanreotide 30 mg treatment and by 38% of patients during lanreotide Autogel treatment (Table 2).

Changes in lanreotide levels during lanreotide 30 mg and lanreotide Autogel injections

During lanreotide 30 mg treatment, the mean lanreotide level, measured 7–14 d after im injections, was greater than 1 ng/ml and did not show any relevant change (*i.e.* steady state) during the last five injections of lanreotide 30 mg (Fig. 2). At the end of lanreotide 30 mg treatment, mean lanreotide levels were higher in patients treated with one injection every

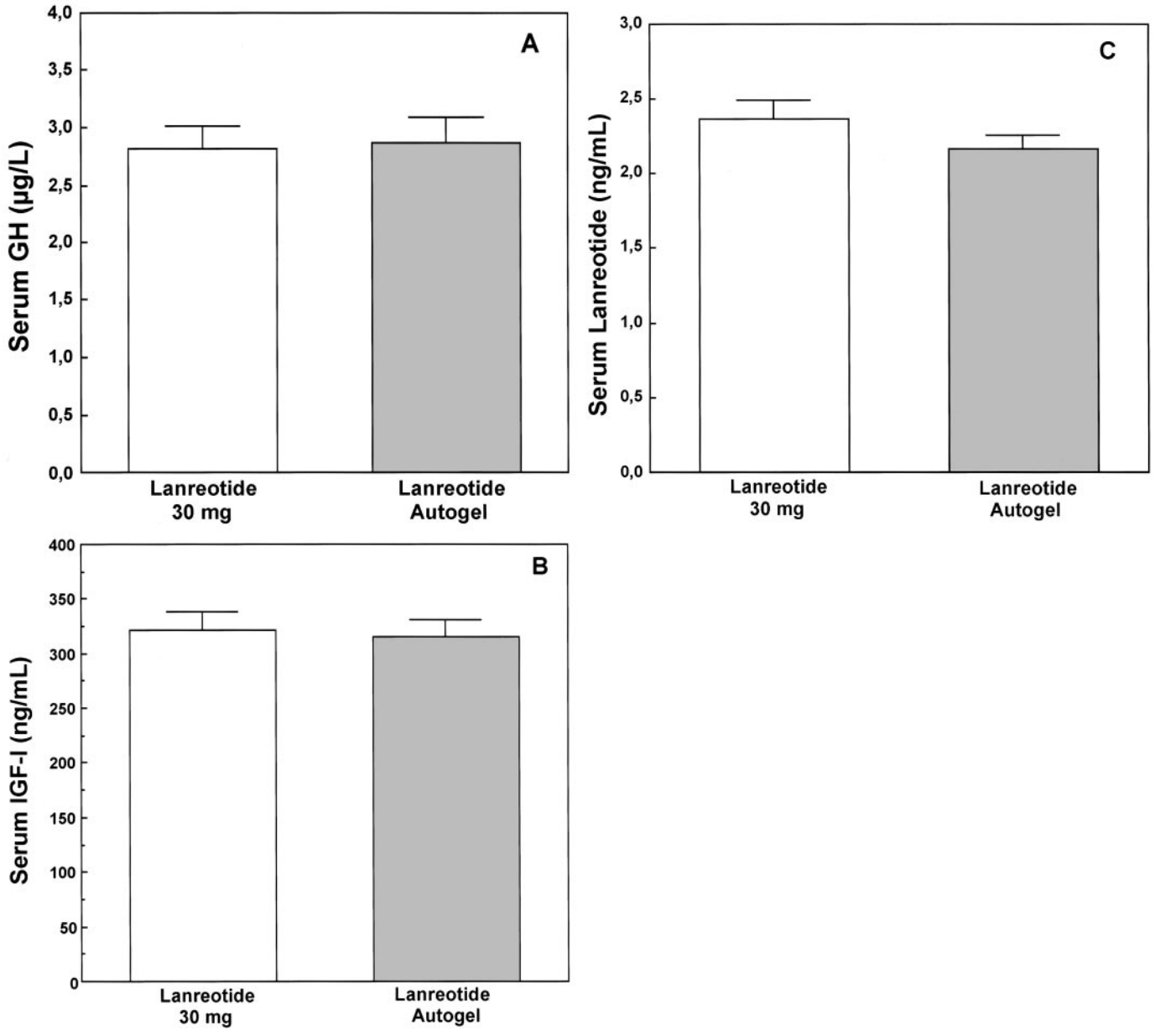

FIG. 1. Mean levels (±SEM) of GH (A), IGF-I (B), and lanreotide (C) in 107 acromegalic patients treated with im lanreotide 30 mg and deep sc lanreotide Autogel injections.

TABLE 1. Plasma GH and IGF-I (mean ± SEM) in acromegalic patients during im lanreotide (30 mg) treatment and after one and three deep sc lanreotide Autogel injections

	Lanreotide (30 mg)	Lanreotide Autogel	
		1st injection	Last injection
GH (ng/ml)	2.82 ± 0.19	3.51 ± 0.28	2.87 ± 0.22
IGF-I (ng/ml)	323 ± 16	345 ± 16	317 ± 15

TABLE 2. Percentage of acromegalic symptoms in patients treated with lanreotide (30 mg) and deep sc lanreotide Autogel injections

	Lanreotide (30 mg)	Lanreotide Autogel
Headaches	27	29
Night sweats	23	21
Asthenia	32	29
Swelling of extremities	34	28
Joint pain	39	38

Percentages are shown.

7 d (3.10 ± 0.25 ng/ml) or 10 d (2.65 ± 0.20 ng/ml) than in those injected every 14 d (1.86 ± 0.12 ng/ml). After lanreotide 30 mg withdrawal, the mean lanreotide levels, measured 28 d after the first deep sc injection of lanreotide Autogel, had decreased in each dose group. The mean lanreotide levels measured 28 d after each subsequent deep sc injection of lanreotide Autogel increased in each group. After three lanreotide Autogel injections, the mean lanreotide levels were not different from the values obtained at steady state with

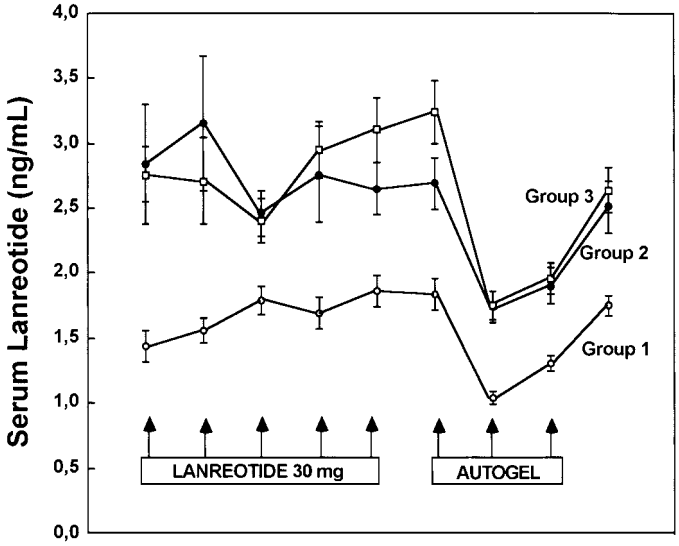

FIG. 2. Mean lanreotide level (±SEM) in acromegalic patients treated with im lanreotide 30 mg injections (group 1, every 14 d; group 2, every 10 d; group 3, every 7 d) and 28-d lanreotide Autogel injections (group 1, 60 mg; group 2, 90 mg; group 3, 120 mg).

TABLE 3. Percentage of gastrointestinal symptoms, local signs at sites of injection, and abnormal gall-bladder echographies in acromegalic patients treated with im lanreotide (30 mg) and deep sc lanreotide Autogel injection

	Lanreotide (30 mg)	Lanreotide Autogel
Gastrointestinal symptoms		
Diarrhea	38	29
Abdominal pain	22	17
Nausea	18	9
Local tolerance		
Pain	5	7
Itching	3	2
Induration	5	7
Gall-bladder echographies		
Lithiasis	27	34
Sludge	11	7

Percentages are given.

lanreotide 30 mg injections (lanreotide 30 mg, 2.37 ± 0.11 ng/ml; lanreotide Autogel, 2.17 ± 0.09 ng/ml; Fig. 1C).

Tolerability of lanreotide Autogel injections

Minor gastrointestinal problems, such as diarrhea, abdominal pain, and nausea lasting less than 72 h, were reported during the study (Table 3). After treatment with lanreotide 30 mg and lanreotide Autogel, diarrhea was reported by 38% and 29% of patients, abdominal pain by 22% and 17% of patients, and nausea by 18% and 9% of patients, respectively. In most patients, these adverse events were mild to moderate. Mild pain, itching, and induration at the site of injection occurred in less than 7% of patients during lanreotide 30 mg or lanreotide Autogel treatment. The prevalence of either gallstones or sludge was 38% for patients receiving lanreotide 30 mg and 41% for patients receiving lanreotide Autogel. Finally, during lanreotide Autogel treatment there was no evidence of significant change in the routine hematological and biochemical parameters evaluated during the study compared with those at the end of treatment with lanreotide 30 mg.

Discussion

The effectiveness of somatostatin analog treatment in acromegalic patients has been found to correlate with the molecular characteristics of the somatotroph cells (9–15) as well as with the plasma concentration of somatostatin analog (3, 13). In clinical studies, control of GH hypersecretion in acromegalic patients responsive to somatostatin analogs has been improved by increasing the dose of sc octreotide (14) or the frequency of im lanreotide 30 mg injections (4–6).

Control of GH hypersecretion during treatment with octreotide LAR or lanreotide 30 mg has been reported to be similar to that obtained during sc octreotide treatment (6, 9, 15–18). In this current study of acromegalic patients treated with lanreotide 30 mg injections every 7–14 d, the mean GH level was less than 2.5 ng/ml in 48% of patients, and there was an age-/sex-normalized IGF-I in 45% of patients. During lanreotide Autogel treatment, the mean GH level was less than 2.5 ng/ml, and IGF-I levels were normalized in 56% and 47% of patients, respectively. During lanreotide 30 mg and lanreotide Autogel treatments, GH hypersecretion was controlled with the mean GH level less than 2.5 ng/ml and an age-sex-normalized IGF-I value (19) in 33% and 39% of patients, respectively. Therefore, this clinical study shows that in patients with GH-secreting pituitary adenomas, deep sc injections of lanreotide Autogel every 28 d are at least as efficacious as im injections of lanreotide 30 mg every 7–14 d in controlling GH hypersecretion.

The mean lanreotide level measured 7–14 d after the last injection of lanreotide 30 mg was significantly higher in the 90 and 120 mg groups than in the 60 mg group. Therefore, differences in lanreotide levels between patients responsive to lanreotide 30 mg suggest that patients in the 60 mg group are more sensitive to lanreotide than those in the 90 and 120 mg groups. Such variable sensitivities of acromegalic patients to somatostatin analogs have been found to correlate with the number, distribution, and activity of somatostatin receptor subtypes on the GH-secreting adenoma (9–11) and the adenylate cyclase activity in somatotroph cells (12).

After long-term lanreotide 30 mg treatment, mean lanreotide levels decrease following withdrawal of lanreotide 30 mg and are less than 1 ng/ml 28 d after the last injection (20). However, the decrease in lanreotide levels is different between groups treated with lanreotide 30 mg every 10 and 14 d, suggesting that the clearance rate of lanreotide may vary in acromegalic patients. This in conjunction with the variable sensitivities described above may explain the variable doses of lanreotide Autogel required to control GH hypersecretion in acromegalic patients.

On the basis of pharmacokinetic studies, the administered doses of lanreotide Autogel were determined according to the dosing interval of lanreotide 30 mg. During lanreotide Autogel treatment, plasma lanreotide levels (measured 28 d after each injection) progressively increased in all groups. However, the steady state for the lanreotide level was not obtained after the first three injections of lanreotide Autogel due to the long half-life of the drug (25–30 d). This pattern

suggests that there is a cumulative effect during the first injections of lanreotide Autogel, as previously shown in acromegalic patients treated with either sc octreotide (21) or im lanreotide 30 mg injections (22). After three deep sc injections of lanreotide Autogel, mean lanreotide levels were significantly different in the 60 mg group and the 90 or 120 mg groups and were similar to the values obtained at steady state with lanreotide 30 mg. Furthermore, during short-term treatment with lanreotide Autogel (administered every month for 3 months), plasma lanreotide levels were higher than 1 ng/ml, enabling lanreotide Autogel to reduce plasma GH and IGF-I concentrations in acromegalic patients responsive to lanreotide 30 mg (22).

Somatostatin analog treatment is well tolerated in most patients. The main side-effects reported by patients are minor gastrointestinal problems, such as diarrhea, abdominal pain, and nausea. In most patients, gastrointestinal side-effects become less frequent during long-term treatment and do not lead to interruption of treatment. In this current study gastrointestinal side-effects reported during lanreotide 30 mg treatment are comparable with those reported in previous studies (4, 5, 7, 8, 22). After the first injection of lanreotide Autogel, there are fewer reported gastrointestinal adverse events (diarrhea, abdominal pain, and nausea) than during long-term lanreotide 30 mg administration. The relatively high frequency of gastrointestinal symptoms reported after im lanreotide 30 mg injections may be explained by the pharmacokinetic profile of the formulation. Lanreotide 30 mg is composed of microparticles containing lanreotide. Plasma lanreotide levels reach a peak 2 h after im injection due to the rapid release of the analog localized at the surface of the copolymer and then decline over 48 h. Subsequently, they increase and then progressively decrease until d 10–14 following injection. Conversely, lanreotide Autogel is an aqueous preparation of lanreotide acetate administered by deep sc injection. Lanreotide levels increase, but the peak lanreotide level is lower than it is with lanreotide 30 mg, and it subsequently decreases over a 28-d period. This might explain why the frequency of gastrointestinal problems reported during lanreotide Autogel treatment seems to be lower than that reported at the beginning of lanreotide 30 mg treatment. During lanreotide 30 mg and lanreotide Autogel treatments, mild and transient pain at the injection site with local itching or induration occur with similar frequency (<7%). The most potentially important adverse event during long-term somatostatin analog administration is an increased tendency for gallstone formation. In this study gallbladder echography performed after three lanreotide Autogel injections did not reveal any significant increase in the presence of gallstones or sludge. Thus, a similar percentage of patients reported mild or moderate side-effects during lanreotide 30 mg and lanreotide Autogel treatments. These results show that lanreotide Autogel is as well tolerated as lanreotide 30 mg in acromegalic patients.

In conclusion, this clinical study shows that when given at the same monthly dose, lanreotide Autogel is at least as efficacious and well tolerated as lanreotide 30 mg in patients with a GH-secreting pituitary adenoma. This new long-acting lanreotide formulation is administered by deep sc injection every 28 d from a small volume, prefilled syringe and is likely to improve the acceptability of medical treatment for acromegalic patients who need long-term somatostatin analog therapy.

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