Sandostatin LAR®: Pharmacokinetics, Pharmacodynamics, Efficacy, and Tolerability in Acromegalic Patients

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Sandostatin LAR® was developed by incorporating octreotide in microspheres of the biodegradable polymer poly(DL-lactide-co-glycolide glucose). One hundred acromegalics, 85 of whom were known to be "responders" to octreotide (subcutaneous [SC] Sandostatin® 0.1 to 0.2 mg three times daily), as measured by mean 12-hour growth hormone (GH) serum concentrations below 5 μg/L, were switched after a washout period of at least 3 days to single doses of 3, 6, 9, 12, 10, 20, and 30 mg Sandostatin LAR®. Octreotide and GH serum concentrations were assessed hourly from 8 AM to 8 PM, during screening, at baseline (after washout), and on days 1 (day of injection), 7, 14, 21, 28, 35, 42 (for doses of 3, 6, 9, and 12 mg), and 60 (for doses of 10, 20, and 30 mg). The pattern of octreotide release was similar for all doses tested. A rapid increase in octreotide serum concentrations was noted after the intramuscular (IM) injection of Sandostatin LAR®, with a peak occurring within 1 hour of injection and followed by a progressive decrease to low octreotide levels within 12 hours. On days 2 through 7, after single doses of Sandostatin LAR®, lower octreotide serum concentrations were recorded. Thereafter, an increase in the serum octreotide concentration occurred and dose-dependent plateau concentrations were observed between days 14 and 42, followed by a progressive decrease from day 42 onward. In the plateau phase (days 14 to 42), daily average octreotide plasma concentrations remained very stable over the 12-hour observation period, comparing well with those seen after continuous SC infusion. The peak level on day 1 (for the 10-, 20-, and 30-mg doses) was lower than plateau octreotide concentrations, and the area under the peak on the Sandostatin LAR® injection day was no greater than 0.5% of the total area under the curve ([AUC] 0 to 60 days). A dose-dependent increase in the octreotide maximum concentration and AUC occurred in the dose range of 10 to 30 mg. There is an almost linear relationship between plateau octreotide concentrations and the dose administered. Plateau octreotide concentrations were approximately 350 ng/L for the 10-mg dose, 750 for the 20-mg dose, and 1,300 for the 30-mg dose. No accumulation of octreotide was noted after repeated injections at 4-week intervals in 40 patients who received up to seven injections of Sandostatin LAR®. Steady-state octreotide serum concentrations were reached after multiple injections (three injections at 4-week intervals) and were higher by a factor of 1.6 in comparison to plateau octreotide levels noted after the first injection. Plateau octreotide concentrations lasting for a period of 20 to 30 days point to once-a-month dosing in long-term treatment. The pattern of GH secretion irrespective of dose showed an initial suppression for 8 to 12 hours, followed by a return to almost preinjection values on days 2, 3, and 7 after the first injection. From days 14 to 42, the maximum suppression of GH secretion was recorded for each dose tested. Reproducible and stable suppression of GH secretion was noted after single-dose administration of 10, 20, or 30 mg and repeated injections of 20, 30, or 40 mg Sandostatin LAR®, and this mirrored the consistent and stable octreotide concentration. A trend toward progressive suppression of GH secretion and insulin-like growth factor-I (IGF-I) serum concentrations was noted during long-term treatment (up to 35 weeks) with repeated (up to seven) IM injections of Sandostatin LAR®. Administered at 4-week intervals, the 20- and 30-mg doses provided a very good clinical control of acromegalic symptoms/signs in all patients, including the "partial responders" (with GH concentrations not suppressed to below 5 μg/L). The local tolerability was very good, with mild to moderate local pain on injection days. Systemic tolerability of Sandostatin LAR®, including gallstone formation, compared well with the SC treatment with Sandostatin®. As a result of the convenience of administration, very good acceptance, very stable and consistent octreotide serum concentrations in long-term treatment, and very good biological and clinical efficacy, it is expected that Sandostatin LAR® will become the medical treatment of choice in acromegalic patients.

ACROMEGALY is the clinical and metabolic syndrome resulting from the hypersecretion of growth hormone (GH) in patients with pituitary GH-secreting adenomas. Exceptionally, the disease occurs secondary to GH hypersecretion produced by a GH-releasing hormone–secreting adenoma. Acral enlargement, bone and soft-tissue overgrowth, and visceromegaly are the major clinical signs of the disease. The increased mortality and morbidity of acromegalic patients are well documented. Premature death occurs from cardiorespiratory complications, metabolic disturbances such as diabetes mellitus, and predisposition to gastrointestinal cancer.[1] Effective treatment reducing GH secretion could reduce mortality related to acromegaly.

The development of octreotide (Sandostatin®, Sandoz, Basel, Switzerland), a specific and potent type 2 somatostatin receptor agonist, opened a new era in the medical therapy for acromegaly. Sandostatin®, like somatostatin, exerts inhibitory effects on the release of pituitary and gastroenteropancreatic hormones, ie, GH, thyrotropin, insulin, glucagon, cholecystokinin, vasoactive intestinal peptide, and gastrin; inhibits gastric acid, pancreatic enzyme

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secretion, and bile flow; prolongs orocecum transit time; and decreases gallbladder contractility. Unlike somatostatin, Sandostatin® inhibits GH preferentially over insulin, and its administration is not followed by rebound hypersecretion of hormones (ie, GH in acromegalics). Owing to its resistance to enzymatic degradation, which mainly accounts for its longer half-life (90 to 100 minutes *v* 1 to 3 minutes for somatostatin), Sandostatin® is usually administered by subcutaneous (SC) injection (at doses of 0.1 to 0.5 mg three times daily).

Results of several long-term multicenter studies[2-5] in acromegalic patients treated with daily doses of SC Sandostatin® ranging from 0.05 to 1.50 mg showed marked and rapid clinical improvement in most patients. Serum GH decreased to less than 5 μg/L in approximately 50% of patients. No rebound GH hypersecretion occurred after discontinuation, and no case of tachyphylaxis or escape was noted. Serum somatomedin-C (insulin-like growth factor-I [IGF-I]) decreased to normal in approximately 50% of patients, with the best results being obtained in patients with microadenomas.[4] Pituitary tumor size reduction by more than 20% of the largest diameter occurred in half of the total number of patients assessed by computed tomography examinations.[2]

Comparisons with bromocriptine showed that Sandostatin® produced greater GH and IGF-I suppression and better clinical results.[6-8]

Besides its very good efficacy, Sandostatin® is a well-tolerated compound. No disturbances of safety tests or liver and renal function were observed. The only consistent adverse events, related to the various inhibitory effects of somatostatin analogs, were transient abdominal discomfort, diarrhea/loose stools, and steatorrhea.[2-5] In a review of five series of reports published in the last 4 years, Ho and Reuten[5] reported an incidence of 22% of newly occurring asymptomatic gallstones in acromegalic patients treated for 3 to 59 months with Sandostatin®. The underlying pathogenic mechanism of gallstones is considered to be stasis and an alteration in bile acid composition, leading to a more lithogenic content of bile. Treatment with ursodeoxycholic acid leads to dissolution of gallstones in most patients.

Since Ikuyama et al[9] and Reubi and Landolt[10] showed that the GH response to Sandostatin® correlates with the somatostatin receptors at the GH-tumor cells, several groups have confirmed that heterogeneity in the response of acromegalic patients to somatostatin analogs is related to the density of somatostatin receptors at the tumor level.[11-14] In addition, in a subset of GH-secreting adenomas, a mutation of the αs-subunit of G protein that activates adenylate cyclase has been reported,[13] suggesting postreceptor changes that might also account for the heterogeneity of responses to Sandostatin®.

Several studies published in the last few years[15-19] showed that Sandostatin® administered by continuous SC pump infusion in comparison to intermittent SC injections produced better suppression of GH and IGF-I serum concentrations, rapid clinical improvement, and shrinkage of GH-secreting adenomas. Christensen et al[15] reported data collected in 10 acromegalic patients investigated before and after continuous SC infusion and then after an equivalent daily dose administered as SC injections three times daily. The continuous infusion resulted in a greater and more stable 24-hour suppression of GH secretion as compared with levels reached at the nadir GH concentration between SC injections. James et al[19] have also shown that a continuous SC infusion at incremental doses (from 0.2 to 1.6 mg/24 h) consistently suppressed GH serum concentrations to below 5 μg/L, with the optimal reduction occurring already at the dose of 0.4 mg/24 h, which provides octreotide serum concentrations of 2,200 ± 320 ng/L. Similar results were reported by Roelfsema et al[18] in a crossover study performed in 10 acromegalics treated with 0.3 mg Sandostatin® either by intermittent three-times-daily injection or SC infusion. Seven patients had normalized IGF-I concentrations during SC infusions versus three patients receiving intermittent treatment. Data on the very good efficacy of Sandostatin® administered by pump infusion stimulated research to develop a new galenical formulation that could ensure long-lasting, sustained, and consistent drug delivery.

An extended-release formulation mimicking the continuous SC infusion of octreotide to be injected monthly would be an obvious improvement in the treatment of acromegalic patients requiring long-term Sandostatin® therapy by twice-daily or three-times-daily dosing. To cover this therapeutic need, Sandostatin LAR® was developed by incorporating octreotide in microspheres of a biodegradable polymer, poly(DL-lactide-co-glycolide glucose). Sandostatin® and Sandostatin LAR® are registered trade names of Sandoz, Ltd, Switzerland. Sandostatin LAR® was developed to provide patients with the convenience of a once-a-month injection and to ensure a stable serum octreotide concentration between injections, sustained GH and IGF-I suppression, good clinical control of symptoms and signs of acromegaly, and improved acceptability and compliance for long-term treatment with Sandostatin®.

The release characteristics and toxicology of Sandostatin LAR® were studied in rats and rabbits. Single intramuscular (IM) injections of Sandostatin LAR® resulted in an initial peak, attributed to drug adsorbed to the surface of microspheres, followed by low concentrations over 1 to 2 weeks and thereafter by sustained octreotide plasma levels over a period of 4 to 6 weeks. After repeated injections at 4-week intervals, consistent and stable plasma concentrations of octreotide were recorded. Toxicological studies performed in rabbits and rats revealed only a very limited, reversible granulomatous myositis at the injection site. The biodegradation of the microspheres is completed within 10 to 12 weeks, and toxicological studies showed that Sandostatin LAR® has low toxicity and good local tolerability.

SUBJECTS AND METHODS

Three single-dose studies were performed as prospective double-blind, randomized, multicenter studies in 100 acromegalic patients who gave their written informed consent to be switched from three-times-daily (0.1 or 0.2 mg) SC treatment with Sandostatin® (to allow intrasubject comparison between the two formulations) to

Sandostatin LAR® 3-, 6-, 9-, and 12-mg doses or 10-, 20-, or 30-mg doses. Patients were selected on the basis of their good tolerability to octreotide, with the mean 12-hour GH serum concentrations below 5 μg/L during treatment with Sandostatin® SC and above 5 μg/L after a washout period of at least 3 days. A longer washout (range, 2 to 10 weeks) was required in some patients treated for more than 1 year with Sandostatin® due to a carryover effect of the SC treatment.

All studies were performed in accordance with the Helsinki Declaration concerning research in humans and amended in Tokyo, Venice, and Hong Kong. Furthermore, these studies were conducted under a US IND, and they follow the US Code of Federal Regulations concerning clinical trials.

The primary efficacy parameter was the mean 12-hour GH serum concentration assessed hourly from 8 AM to 8 PM on selected days: day of screening (during SC treatment), baseline (after washout), days 1 (day of Sandostatin LAR® injection), 7, 14, 21, 28, 35, 42, and 60. Assessments of octreotide serum concentrations were made on the same days and time points to define the pharmacokinetic profile of Sandostatin LAR®.

Secondary parameters of efficacy were (1) IGF-I serum concentrations assessed on the day of screening, baseline, and days 14, 28, and 42 by two samplings (at 8 and 9 AM), and (2) clinical symptoms/signs of acromegaly (the following were selected: headache, perspiration, paresthesias, fatigue, osteoarthralgia, and carpal tunnel syndrome) rated on a five-point scale from 0 (absent) to 4 (severe) and incapacitating.

All patients but two who violated the protocol of the double-blind, single-dose studies were admitted in extension studies.

The extension studies were prospective open-label studies. They involved administration of six injections of Sandostatin LAR® over a 28-week period, allowing investigators to titrate patients to their optimal therapeutic response (using doses of 20, 30, or exceptionally 40 mg). An interval of 28 days between injections was considered optimal for providing consistent steady-state concentrations of octreotide, based on pharmacokinetic simulation of single-dose profiles and considering the linearity of pharmacokinetics of octreotide.

The criteria of efficacy used in the extension studies were identical to those established for the double-blind studies, except that GH serum concentrations were assessed over 8 hours (from 8 AM to 4 PM) by hourly sampling on days 1, 28, 42, and 60 after the first injection in the extension study and thereafter on days 1 and 28 after each subsequent injection (aiming to suppress GH secretion consistently to a mean concentration of below 5 μg/L).

The tolerability of Sandostatin LAR® was assessed by recording all adverse events reported spontaneously or elicited by inquiry or observation. The local tolerability at the injection site (the gluteal muscle) was recorded by inquiry/observation of pain, rash, and swelling, and was rated absent, mild, moderate, or severe. Assessments were performed at each visit in the clinic for GH/octreotide profiles.

Safety was assessed before (at baseline) and at the end of the observation period of both the single-dose, double-blind studies and open-extension studies by physical examination, recording of vital signs, hematology, and blood chemistry (including hemoglobin A_{1C} as a global test for glucose tolerance), ultrasonography of the biliary tract, and assessments of thyrotropin, free and total thyroxine and triiodothyronine.

GH and IGF-I serum concentrations for all patients were assessed in a central laboratory. A fully validated, highly specific, double-monoclonal-antibody, commercially available immunoassay ("Delfia" kit; Wallac, Turku, Finland) was used to assess GH serum concentrations. An assessment of 12-hour GH mean concentrations was also made in six healthy volunteers to define "normal" GH serum concentrations. In all six subjects, mean 12-hour GH concentrations were below 1 μg/L.

Serum IGF-I concentrations were assessed by radioimmunoassay using the commercial kit developed by the Nichols Institute (San Juan Capistrano, CA). Acid-ethanol extraction was performed for removing the IGF binding proteins known to interfere with IGF-I concentrations measured by radioimmunoassay.

Besides the assessment of IGF-I serum concentrations in acromegalics treated with Sandostatin LAR®, the central laboratory assessed samples from 103 healthy volunteers aged 20 to over 60 years. IGF-I concentrations measured were superimposable (normal range, 65 to 500 μg/L) to those provided by the Nichols Institute.

Serum octreotide concentrations were assessed by a fully validated radioimmunoassay using a commercially available kit (ANAWA, Wangen, Switzerland).

RESULTS

Overview of Pharmacokinetic/Pharmacodynamic Data Recorded in Acromegalic Patients

A consistent pattern of octreotide release from the polymer matrix of Sandostatin LAR® was documented in all studies and for all dose levels investigated in acromegalic patients. A rapid increase in octreotide serum concentrations was noted after IM injection of Sandostatin LAR®, with a peak occurring within 1 hour after the injection

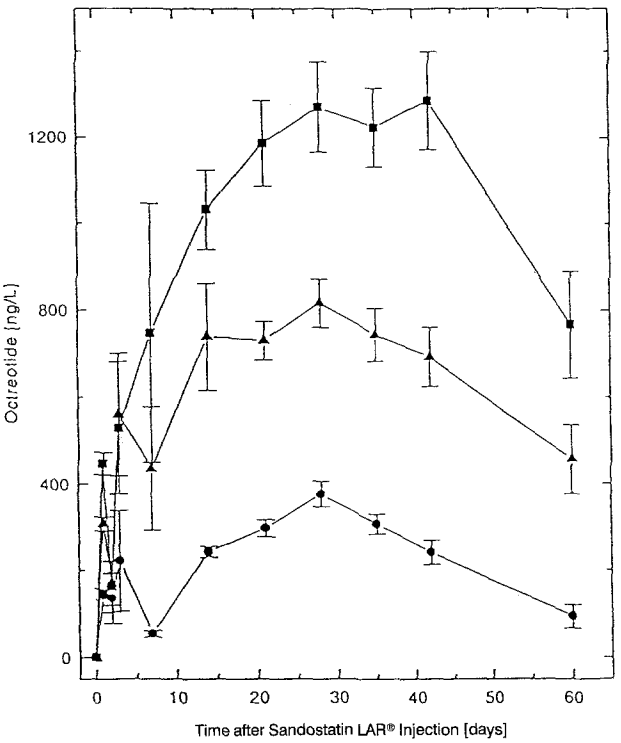

Fig 1. Mean ± SEM octreotide concentrations *v* time profiles (on days 1, 7, 14, 21, 28, 35, 42, and 60) after administration of single doses of 10 mg (●, n = 16), 20 mg (▲; n = 39), or 30 mg (■; n = 37) Sandostatin LAR® to acromegalic patients. Each point is the mean of 12-hour mean concentrations per patient.

followed by a progressive decrease to low octreotide levels within 12 hours. On days 2 through 7, after single doses of Sandostatin LAR®, octreotide serum concentrations were at lower levels. Thereafter, an increase in serum octreotide concentrations occurred, and dose-dependent plateau concentrations were observed between days 14 and 42 followed by a progressive decrease from day 42 on. In the plateau phase (days 14 to 42), the daily average plasma concentrations remained very stable over the 12-hour observation period, similar to those seen after SC continuous infusion (Figs 1 and 2).

The height of the octreotide peak on day 1 for all doses tested was lower than the plateau concentrations, and the area under the peak on the day of injection of Sandostatin LAR® was not larger than 0.5% of the total area under the curve ([AUC] 0 to 60 days).

A dose-dependent increase of the maximum concentration and AUC of octreotide was recorded in the dose range between 10 and 30 mg. Whereas the maximum concentration and plateau octreotide concentrations increased almost linearly with dose, the AUC increased slightly more than proportionally with dose.

The key pharmacokinetic parameters observed are summarized in Table 1.

It has also been observed that:

- No drug burst occurred (after any of the doses tested: 3, 6, 9, 12, 10, 20, and 30 mg).
- The pattern of octreotide release was similar for all tested doses.
- The very low fluctuations of octreotide serum concentrations over the 12-hour profiles on days 7, 14, 21, 28, 35, 42, and 60 after administration of Sandostatin LAR® mim-

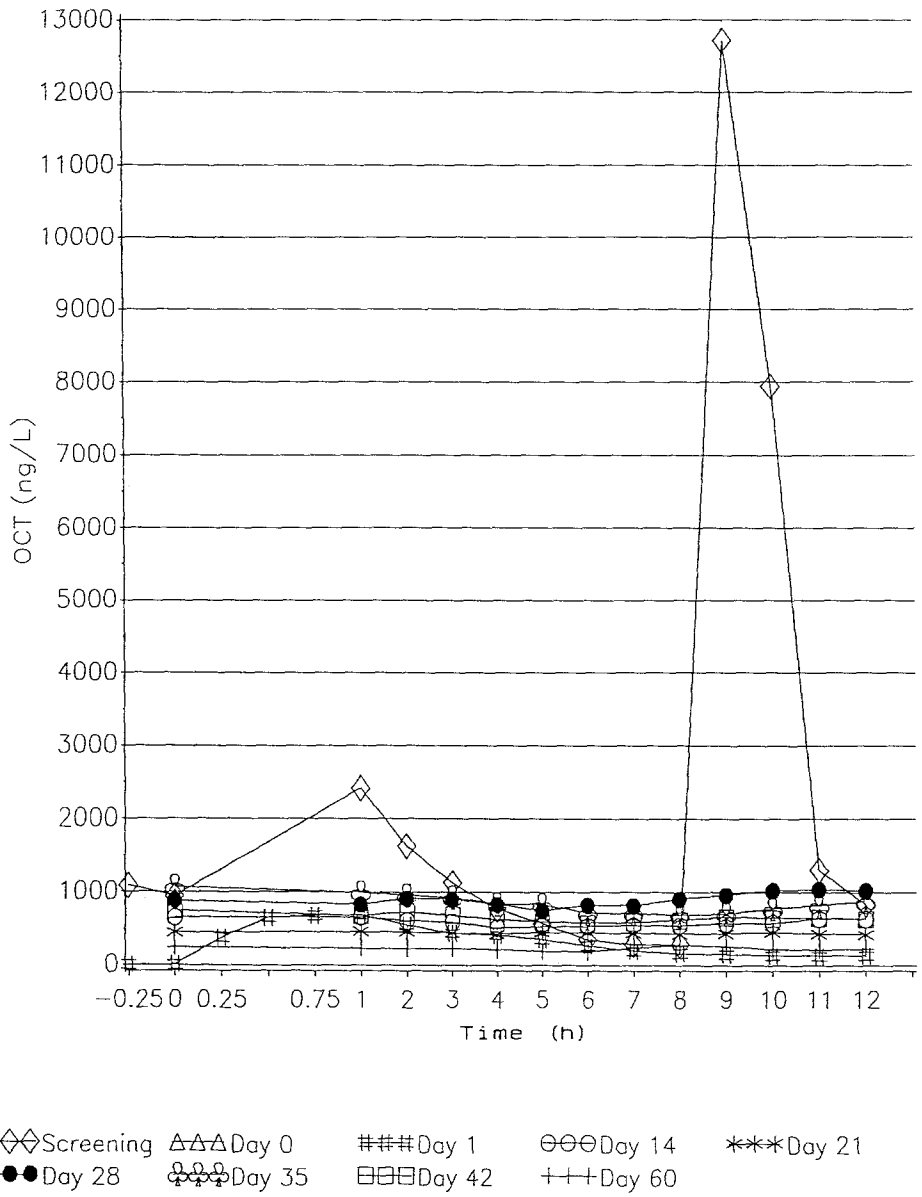

Fig 2. 12-Hour octreotide profile on the screening day (during SC treatment with 0.100 mg three times daily Sandostatin®), day 0 (after washout), day 1 (day of injection of Sandostatin LAR® 20 mg), and days 14, 21, 28, 35, 42, and 60 after the first injection of Sandostatin LAR® in a representative patient.

Table 1. Mean ± SD Pharmacokinetic Parameters of Octreotide Assessed Over a Period of 60 Days

	Dose of Sandostatin LAR®		
	10 mg (n = 16)	20 mg (n = 39)	30 mg (n = 37)
t_{max} (d)	28 ± 10	28 ± 11	34 ± 17
C_{max} (ng/L)	387 ± 107	1,126 ± 749	1,935 ± 1,430
C_{max}/D (ng/L)	39 ± 11	56 ± 38	66 ± 48
$AUC_{0\text{-}60\ days}$ (d ng/L)	13,412 ± 3,417	35,737 ± 16,243	61,494 ± 28,245
$AUC_{0\text{-}60\ days}$/D (d ng/L)	1,341 ± 342	1,787 ± 812	2,050 ± 942
Plateau duration (d)	19.3 ± 10.2	18.5 ± 10.1	18.5 ± 9.8
Relative bioavailability (%)*	31	39	50

*Relative bioavailability with respect to SC three-times-daily treatment; values are the geometric mean.

Abbreviations: t_{max}, time to maximum concentration; C_{max}, maximum concentration; C_{max}/D, maximum concentration normalized on dose; $AUC_{0\text{-}60\ days}$, area under the curve from day 0 to day 60; $AUC_{0\text{-}60\ days}$/D, AUC normalized on dose. Plateau duration is the duration during which the concentrations were above 80% of C_{max}.

icked the stable octreotide profile seen during Sandostatin® infusion at constant dose. During the plateau phase (days 14 through 42), peak-trough fluctuation was 25%, as compared with 200% after intermittent SC injections of Sandostatin®. The AUC fluctuation was between 5% and 10%, as compared with 40% after SC three-times-daily injections.

- Plateau octreotide concentrations over a period of 20 to 30 days indicated a once-a-month dosing regimen during long-term treatment.
- There was an almost linear relationship between plateau octreotide concentrations and the dose administered.
- Steady-state octreotide serum concentrations were reached after multiple injections (three injections at 4-week intervals) and were higher by a factor of 1.6 as compared with plateau octreotide levels noted after the first injection.
- No relevant further accumulation of octreotide was noted after repeated injections at 4-week intervals.
- A very low intrasubject variability and an acceptable (35% to 60%) intersubject variability of octreotide concentrations were noted.
- Octreotide concentrations recorded after single and repeated injections of 20- and 30-mg doses were in the required therapeutic range for octreotide in acromegalic patients (1,000 to 3,000 ng/L). Octreotide serum concentrations recorded after administration of the 10-mg dose (less than 500 ng/L) limit its use to patients very sensitive to octreotide.

A consistent pattern of suppression of GH secretion was recorded in acromegalic patients treated with single doses of 10, 20, or 30 mg Sandostatin LAR®. A rapid, short-lasting suppression of serum GH concentrations similar to that noted in patients receiving a SC injection of Sandostatin® occurs on the day of the injection. This initial suppression of GH secretion lasts for 8 to 12 hours and is followed in many patients by a return to almost preinjection values on days 2, 3, and/or 7. From day 14 to day 42, a maximal suppression of GH secretion lasting at least 4 weeks was recorded for each dose tested (Figs 3 and 4).

The main pharmacodynamic parameters evaluated in single-dose studies using the 10-, 20-, and 30-mg doses of Sandostatin LAR® are shown in Table 2.

A stable suppression of GH secretion was noted after repeated injections (up to seven) of Sandostatin LAR® administered at 4-week intervals (starting with the third injection). A typical example is shown in Fig 5 for the mean GH and octreotide concentrations on days 1 and 28 after each injection over the entire observation period.

The pharmacokinetic/pharmacodynamic profile of Sandostatin LAR® shows that this new galenical formulation exhibits definite advantages over the SC three-times-daily treatment with Sandostatin® in acromegalic patients. Suppression of GH secretion is more consistent, and the daily fluctuations are very limited. Based on pharmacokinetic/pharmacodynamic data, 20 or 30 mg Sandostatin LAR® administered once a month are the recommended doses. The 10-mg dose could be used only in patients who show a marked suppression of GH secretion during SC Sandostatin® 0.1-mg three-times-daily treatment.

Efficacy of Sandostatin LAR® in Acromegalic Patients

All patients but 15 showed a suppression to below 5 μg/L on SC three-times-daily Sandostatin® treatment. These pa-

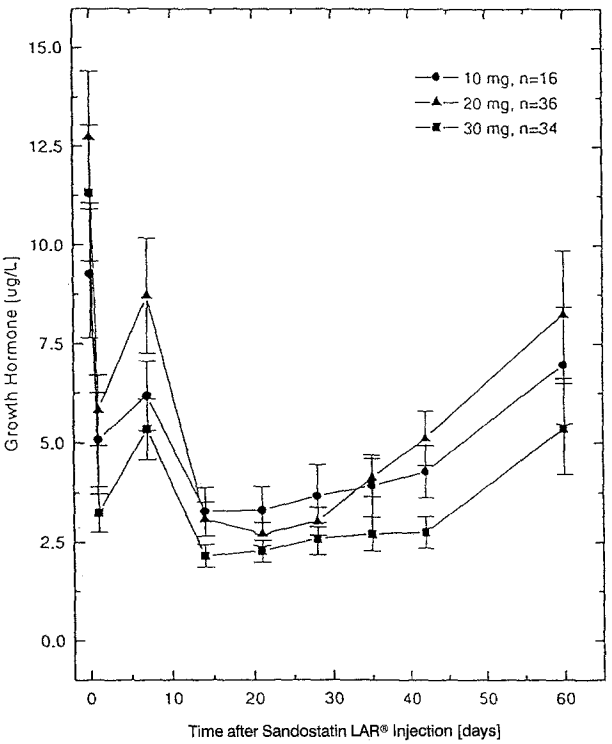

Fig 3. Mean ± SEM GH concentrations v time profiles (on days 1, 7, 14, 21, 28, 35, 42, and 60) after administration of single doses of 10, 20, or 30 mg Sandostatin LAR® to acromegalic patients. Each point is the mean of 12-hour mean concentrations per patient.

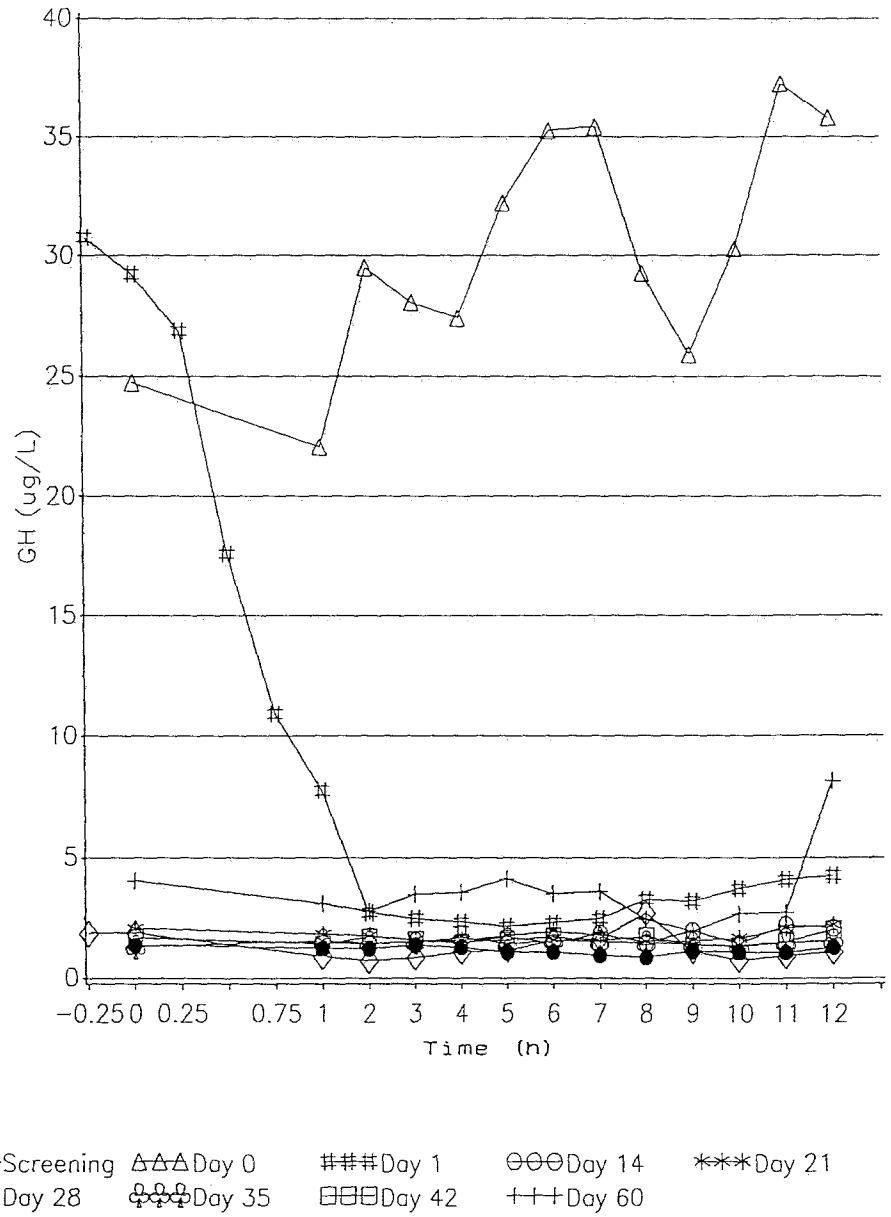

Fig 4. 12-Hour GH profile on the screening day (during SC treatment with 0.100 mg three times daily Sandostatin®), day 0 (after washout), day 1 (day of injection of Sandostatin LAR® 20 mg), and days 14, 21, 28, 35, 42, and 60 after the first injection of Sandostatin LAR® in a representative patient.

tients were considered "responders" to octreotide treatment, whereas patients who showed a marked suppression of GH secretion to at least 50% of their pretreatment concentrations but not below 5 µg/L were considered "partial responders."

Results of the mean 12-hour GH concentrations at screening (during SC treatment with Sandostatin®) clearly showed that the population of responder acromegalics was heterogeneous. Although the majority of patients had mean GH concentrations below 5 µg/L, some had concentrations below 2 µg/L.

In the single-dose, double-blind studies performed with 10, 20, and 30 mg Sandostatin LAR® in 93 patients (15 partial responders and 78 responders), a suppression of GH mean concentrations below 5 or 2 µg/L was recorded, as shown in Table 3.

Patients treated with repeated injections of Sandostatin LAR® at 4-week intervals with individualized doses of 20, 30 (in responder patients), or 40 mg (in partial responder patients) showed a consistent suppression of GH 8-hour mean concentrations to below 5 µg/L. In 80 of 93 patients, a consistent suppression to below 5 µg/L was recorded after administration of Sandostatin LAR® for up to seven injections. In 13 partial responder patients, the mean GH serum concentrations decreased progressively during treatment, but were still above 5 µg/L at the end of the 9-month observation period.

A suppression of GH mean concentrations to below 2 µg/L was recorded in 62 of 78 (79.5%) responder patients, and a full normalization of IGF-I serum concentrations was recorded in 53 of 78 (68%) responder patients.

It has been observed that the IGF-I concentration was

Table 2. Mean ± SD Pharmacodynamic Parameters of Octreotide in the Inhibition of GH Secretion Over a Period of 60 Days

	Dose of Sandostatin LAR®		
	10 mg (n = 13)	20 mg (n = 36)	30 mg (n = 34)
t_{min} (d)	23 ± 16	19 ± 12	22 ± 15
C_{min} (μg/L)	2.7 ± 1.9	2.1 ± 1.4	1.6 ± 1.2
Duration below 5 μg/L (d)	40.7 ± 20.6	38.2 ± 22.1	48.6 ± 15.8
Duration below 2 μg/L (d)	10.0 ± 12.2	14.6 ± 20.5	25.5 ± 23.2
E_{max} (%)	66.5 ± 20.8	78.4 ± 14.9	79.0 ± 16.8
E-$AUC_{0\text{-}60\ days}$ (d%)	2,735 ± 1,242	3,285 ± 1,259	3,810 ± 1,171
Plateau duration >80% E_{max} (d)	22.8 ± 15.9	30.0 ± 16.7	37.6 ± 16.8

Abbreviations: t_{max}, time of maximum inhibition; C_{min}, minimum GH concentration; duration below 5 μg/L, time duration during which GH concentrations were below a given level; E_{max}, baseline corrected maximum effect; E-$AUC_{0\text{-}60\ days}$, area under the effect *v* time curve; plateau duration >80% E_{max}, duration during which inhibition was greater than 80% of E_{max}.

suppressed to within the normal range even in some patients who did not show a normalization during the SC treatment (data not shown).

Besides the marked suppression/normalization of GH and IGF-I serum concentrations, all patients, including the partial responders, showed a marked clinical improvement of all symptoms/signs. In addition, an improvement of the facial appearance, soft-tissue thickening, and capacity to cover professional and family tasks was recorded. A marked improvement in attention, concentration, and memory was noted by two students included in the study. At the end of the 9-month treatment, 32 of 88 patients who received seven injections of Sandostatin LAR® were asymptomatic.

Shrinkage of the GH-secreting adenomas was noted in three patients with microadenomas and in three patients with macroadenomas (of 18 investigated patients) within 6 months of treatment.

The systemic tolerability of Sandostatin LAR® was good, with the following adverse events recorded in the 93 patients treated with doses of 10, 20, or 30 mg Sandostatin LAR® in the single-dose, double-blind studies: episodic abdominal pain, 30 of 93 (32%) patients; diarrhea, 42 of 93 (45%) patients; flatulence, 33 of 93 (35%) patients; steatorrheic stools, nine of 93 (10%) patients; nausea, nine of 93 (10%) patients; vomiting, seven of 93 (8%) patients; and hair loss (transient), eight of 93 (9%) patients.

Most adverse events were mild and short-lasting (1 to 2 days). The prevalence of adverse events decreased markedly and progressively during extension of the treatment by up to 9 months. The local tolerability at the injection site was very good, with 26 of 93 (28%) patients reporting mild/moderate short-lasting pain and three of 93 (3%) showing slight swelling after the first injection of Sandostatin LAR®. Mild pain, exceptionally occurring swelling (two patients), and rash (one patient) on the day of injections were observed during long-term treatment.

No impairment of the safety tests was noted, except for a transitory anemia in 32 of 93 patients recorded after the repeated blood sampling for 10 profiles (12-hour) of GH/octreotide in the double-blind studies. When treated with iron-containing preparations, anemia improved/disappeared in most patients in the follow-up months.

Glucose tolerance was not impaired. Of the five patients with diabetes mellitus at entry, one patient improved markedly, two showed a slight worsening, and two did not show any changes during the 9-month observation period.

The evaluation of thyrotropin, total and free thyroxine and triiodothyronine serum concentrations did not show any impairment of thyroid function during the 9-month treatment with Sandostatin LAR®.

Repeated echographic examinations of the gallbladder region showed the following newly occurring abnormalities: asymptomatic gallstone in one patient, microlithiasis in three patients, sediment in 10 patients, sludge in six

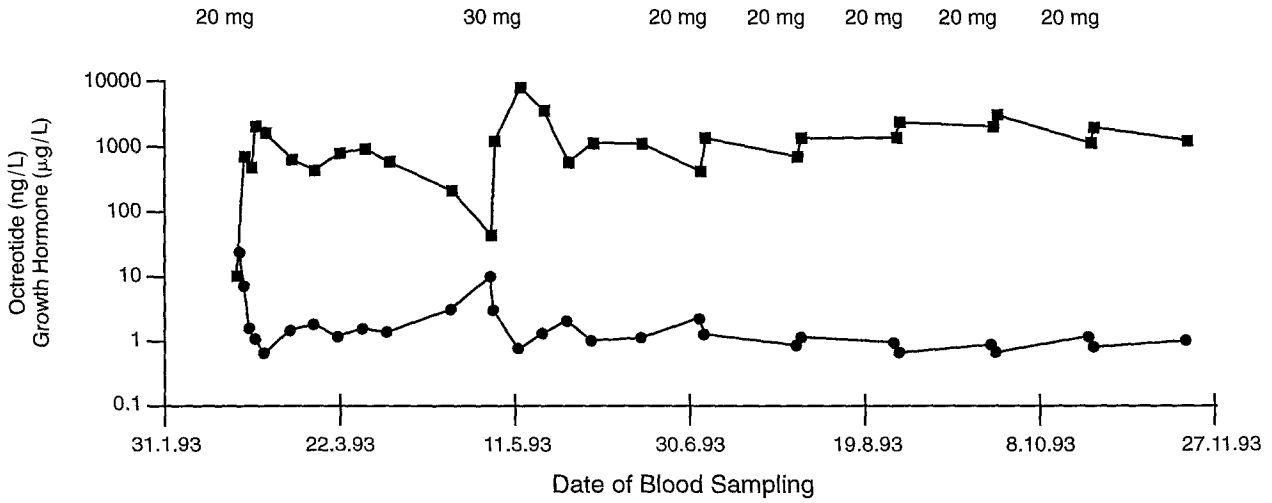

Fig 5. Octreotide (■) and GH (●) concentrations (each point is the mean of 12-hour data recorded by hourly sampling from 8 AM to 8 PM after the first injection, or of 8-hour data recorded from 8 AM to 4 PM after the second to seventh injection) in a representative patient.

Table 3. Number of Patients With a 12-Hour Mean GH Serum Concentration Below 5 and 2 μg/L in the 10-, 20-, and 30-mg Dose Group

GH Mean Concentrations	Responder Patients			All Patients		
	10 mg (n = 11)	20 mg (n = 34)	30 mg (n = 33)	10 mg (n = 16)	20 mg (n = 39)	30 mg (n = 38)
<5 μg/L	11/11	34/34	33/33	13/16	34/39	33/38
<2 μg/L	7/11	21/34	23/33	7/16	21/39	23/38

patients, biliary duct dilatation in two patients, and gallbladder dilatation in five patients.

DISCUSSION

The treatment of choice for patients with acromegaly is transsphenoidal adenomectomy, which can be curative in patients with microadenomas. In acromegalics with GH-secreting macroadenomas, the surgical cure rate, although limited, can be improved by presurgical treatment with Sandostatin®, which can reduce the consistency of the tumor and facilitate surgical removal.[20] In patients with only partial removal of the tumor, radiotherapy of the residual tumor is performed. Since the effectiveness of radiotherapy is sometimes only evident as late as 10 years after its application and since in many patients a secondary hypopituitarism also occurs, medical therapy with Sandostatin® 0.1 to 0.5 mg three times daily has become in medical practice the treatment of choice in patients who fail to be cured by surgery or in newly diagnosed elderly acromegalic patients.

Sandostatin LAR® can replace three-times-daily SC injections by an IM injection at 4-week intervals to improve the acceptability of long-term therapy in acromegalics. In addition, by releasing consistent concentrations of serum octreotide and by producing a consistent suppression of GH secretion, Sandostatin LAR® appears to be as effective as SC infusions of Sandostatin® and more effective than intermittent SC administration. Indeed, in the patients switched from SC treatment to Sandostatin LAR®, suppression of GH secretion and serum IGF-I concentrations and the clinical improvement have been either as good as or better than with Sandostatin® SC. A larger number of patients showed a normalization of serum IGF-I concentrations and a clinical improvement. Beyond the improvement/disappearance of symptoms/signs of acromegaly, some patients have become asymptomatic.

The gastrointestinal adverse events recorded—diarrhea, flatulence, abdominal pain—in general have been mild or moderate and episodic. These adverse events have not led to any patients' withdrawal from treatment with Sandostatin LAR®. With only a newly occurring asymptomatic gallstone in one patient, microlithiasis in three patients, and sediment or sludge in 16 patients, it appears that Sandostatin LAR® can be administered safely to patients with this very severe disease. Equally, the absence of impairment of thyroid function, good tolerability at the injection site, and excellent patient acceptability and compliance with the once-a-month injections for this disease requiring long-term treatment support the recommendation that patients can be safely switched from SC Sandostatin® to Sandostatin LAR® treatment. One could also recommend that medical treatment with Sandostatin LAR® be initiated in newly diagnosed acromegalic patients either as a presurgical treatment or as a first-line therapy in elderly patients or in those for whom surgery or radiotherapy are contraindicated.

In conclusion, Sandostatin LAR® is a new galenical formulation of octreotide, which when injected IM at 4-week intervals:

- Delivers consistent and therapeutic serum octreotide concentrations
- Suppresses GH secretion to below 5 or 2 μg/L (in very sensitive patients to below 1 μg/L)
- Suppresses/normalizes serum IGF-I concentrations
- Improves/leads to the disappearance of symptoms/signs of acromegaly
- Does not increase the incidence of adverse events, including newly occurring gallstones, as compared with the SC treatment.

Patients clinically and biologically well controlled with a daily dose of Sandostatin® SC 0.3 to 0.6 mg can be switched to Sandostatin LAR® without any discontinuation of the SC therapy. Administration of three doses of 20 mg Sandostatin LAR® at 4-week intervals is recommended for reaching steady-state octreotide serum concentrations. Thereafter, the dose of Sandostatin LAR® is increased or decreased depending on the clinical outcome, suppression of serum GH concentrations, and normalization of serum IGF-I concentrations. Patients not clinically and biologically controlled (GH concentrations above 5 μg/L) by the 20-mg dose of Sandostatin LAR® should receive a higher dose at 4-week intervals. Patients whose GH concentrations have been consistently below 1 μg/L, whose serum IGF-I concentrations have been normalized, and who have reported the disappearance of most symptoms/signs of acromegaly during the 3-month treatment with the 20-mg dose at 4-week intervals could then be downtitrated to the 10-mg dose at 4-week intervals. It is recommended that the suppression of GH secretion and IGF-I concentrations be checked, as well as the clinical symptoms/signs, in acromegalic patients after downtitration to this low dose of Sandostatin LAR®.

Thus, Sandostatin LAR® is indicated in patients who are on SC three-times-daily treatment with Sandostatin® following unsuccessful transsphenoidal surgery and before irradiation of the remnant GH-secreting tumor can become effective, and as first-line therapy in acromegalic patients in whom surgery and/or radiotherapy is contraindicated.

Because of the convenience of administration, excellent acceptance by patients, and very consistent octreotide serum concentrations delivered over long-term treatment, it is expected that Sandostatin LAR® will provide significantly improved medical management of patients with acromegaly.

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