Sandostatin® LAR®: A Promising Therapeutic Tool in the Management of Acromegalic Patients

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A stable and sustained suppression of growth hormone (GH) secretion was noted in 101 patients treated long term with individual doses (20 and 30 mg in 89 patients, 40 mg in 12 patients) of Sandostatin® LAR® (Sandoz Pharma Ltd, Basel, Switzerland). Doses of 20 mg and 30 mg at 4-week intervals delivered average octreotide concentrations of 1,348 ± 483 ng/L and 2,631 ± 1,026 ng/L, respectively, in steady-state conditions and provided adequate control of patients who had been well controlled during treatment with 0.1 mg and 0.2 mg thrice-daily subcutaneous (SC) Sandostatin®. Suppression of GH serum concentrations to less than 5 μg, 2 μg, and even 1 μg/L was recorded in more patients and more consistently during long-term treatment with Sandostatin® LAR® than Sandostatin®. A marked decrease or even a normalization of insulin-like growth factor-1 (IGF-1) serum concentrations was observed after the first double-blind 10-, 20-, or 30-mg dose of Sandostatin® LAR®. A progressive improvement was recorded during long-term treatment, with normalization of IGF-1 serum concentrations in 65.3% of patients. A marked clinical improvement was observed in parallel, with 36 of 101 patients (35.6%) becoming asymptomatic after the nineteenth injection of Sandostatin® LAR®. A greater than 20% shrinkage of the GH-secreting adenoma was also recorded in 12 of 14 patients treated with Sandostatin® LAR® after receiving only 2 to 4 weeks of treatment with SC Sandostatin® and in 11 of 18 patients receiving Sandostatin® LAR® as adjuvant therapy after failure of surgery. The systemic tolerability of Sandostatin® LAR® was good, and most adverse events were mild and short term (1 to 2 days). No impairment of thyroid function was detected. Newly occurring gallstones were recorded in four of 101 patients and microlithiasis in four of 101 after up to 30 months of treatment with Sandostatin® LAR®. Due to its excellent efficacy, good tolerability, convenience of administration, and acceptability by patients, Sandostatin® LAR® is considered a promising therapeutic tool in the management of acromegalic patients.

ACROMEGALY is a chronic progressive disease caused by the tumoral hypersecretion of growth hormone (GH). Although the disease progresses slowly, increased mortality in acromegalic patients resulting from cardiovascular and respiratory diseases, and an increased prevalence of malignancy, justify early and effective treatment of patients. The therapeutic options available include surgical excision and/or radiotherapy of the GH-secreting tumor and medical treatment. During the last decade, the need for an effective medical treatment in patients in whom surgery is contraindicated, in patients in whom surgery has proved not to be curative, and in those awaiting the beneficial effects of radiotherapy, has led to the extensive use of Sandostatin® (Sandoz Pharma Ltd, Basel, Switzerland) by endocrinologists. More recently, the inconvenience of twice- or thrice-daily therapeutic regimens with the conventional subcutaneous (SC) formulation of Sandostatin® has been overcome by the development of Sandostatin® LAR®, a new formulation of Sandostatin®. This consists of octreotide incorporated into microspheres of the biodegradable polymer, poly(DL-lactide-co-glycolide-glucose) and has been shown to be effective following monthly intramuscular (IM) injections.

The pharmacokinetic/pharmacodynamic profile, efficacy, and tolerability of single doses of Sandostatin® LAR® has already been reported for 100 acromegalic patients.[1] It has been shown that the pattern of octreotide release was similar for all doses tested. A rapid increase in octreotide serum concentrations was noted after 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®, low 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), average daily octreotide plasma concentrations remained stable over the 12-hour observation period and were comparable to 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] for 0 to 60 days). Plateau octreotide concentrations were approximately 350 ng/L for the 10-mg dose, 750 ng/L for the 20-mg dose, and 1,300 ng/L for the 30-mg single dose. 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[1] as illustrated in Fig 1 in a representative patient who received a 30-mg dose of Sandostatin® LAR®. We now report the

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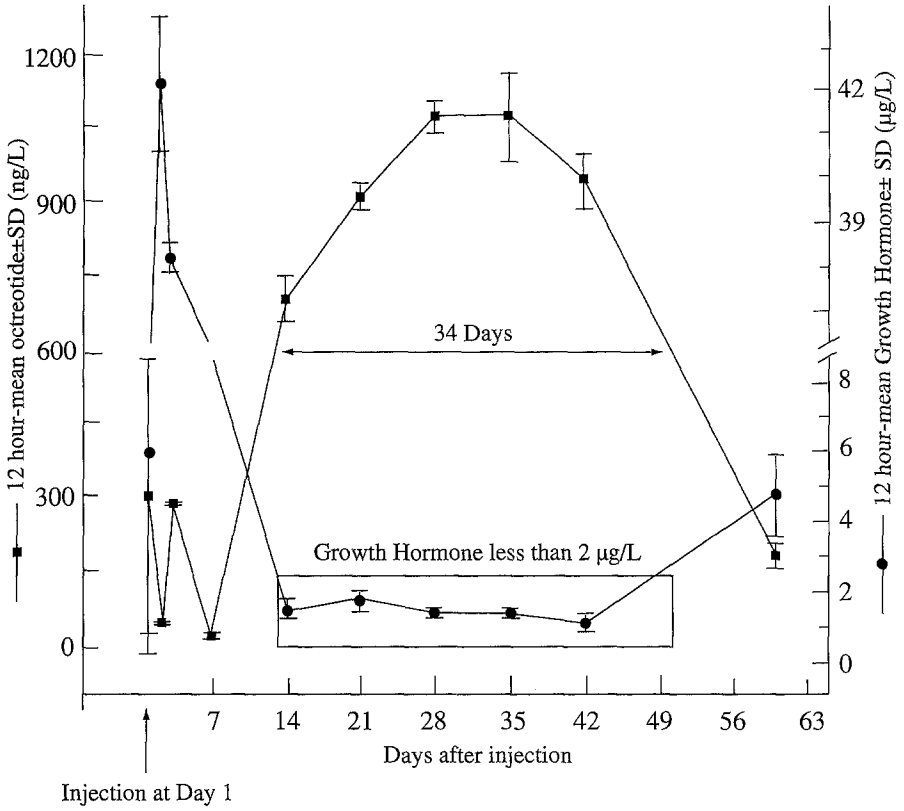

Fig 1. The 12-hour mean octreotide and GH concentrations after a single IM injection of 30 mg Sandostatin® LAR® administered to an illustrative acromegalic patient; n = 13 samples per 12-hour profile, assessed from 8 AM to 8 PM on days 1, 7, 14, 21, 28, 35, 42, and 60.

results recorded in ongoing long-term studies with Sandostatin® LAR® in a total of 101 acromegalic patients.

SUBJECTS AND METHODS

One hundred one acromegalic patients, of whom 89 had completed the single-dose, double-blind, prospective randomized multicenter studies with 10, 20 and/or 30 mg Sandostatin® LAR®, gave written informed consent and entered open-label studies in which they were treated with initially six, followed by 12, and thereafter by nine injections of Sandostatin® LAR® administered at individual doses. All patients were initially treated with 0.1 or 0.2 mg SC thrice-daily conventional Sandostatin® to assess their response to octreotide. Eighty-three of 101 patients were considered good responders to SC Sandostatin® treatment, as their 12-hour mean GH serum concentrations were suppressed to less than 5 μg/L, whereas the other 18 of 101 patients were only partial responders with mean GH serum concentrations suppressed to at least 50% of their initial pretreatment levels, but not below 5 μg/L. During long-term treatment, the efficacy of Sandostatin® LAR® was assessed by the 8-hour mean GH concentration (assessed by hourly sampling on days 1 and 28) after the first six open-label Sandostatin® LAR® injections and thereafter by the 8-hour mean GH concentrations on the last day (day 28) preceding injection in the subsequent extension studies. Serum concentrations of insulin-like growth factor (IGF-1) were also assessed on the days on which GH profiles were recorded. 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), were rated at each visit preceding the subsequent injection in the open extension studies.

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 profiles. Safety was assessed before (at baseline) and at the end of the observation period in each study by physical examination, recording of vital signs, hematology and blood chemistry (including hemoglobin A_{1C} as a global test for glucose tolerance), assessments of thyrotropin, free and total thyroxine, and triiodothyronine concentrations, and ultrasonography of the biliary tract. GH and IGF-1 serum concentrations for all patients were assessed in a central laboratory. A fully validated, highly specific double monoclonal antibody immunoassay (Delfia kit; Wallac, Turku, Finland) was used to assess GH serum concentrations. Serum IGF-1 concentrations were assessed by radioimmunoassay using the commercial kit developed by the Nichols Institute (San Juan Capistrano, CA). Acid-ethanol extraction was performed to remove the IGF-binding proteins known to interfere with IGF-1 concentrations measured by radioimmunoassay.

RESULTS

A stable and sustained suppression of GH secretion was noted in all patients during long-term treatment with individual doses (20 and 30 mg in 89 patients, 40 mg in 12 patients) of Sandostatin® LAR®. The limited daily fluctuations of GH serum concentrations seen during the plateau phase (days 14 to 42) after the first injection[1] were also observed during long-term treatment as shown in two representative patients on days 1 and 28 after the first, second, fourth, and sixth injections of Sandostatin® LAR® in the first open extension study (Figs 2 and 3). The consistency of GH suppression is also demonstrated in Fig

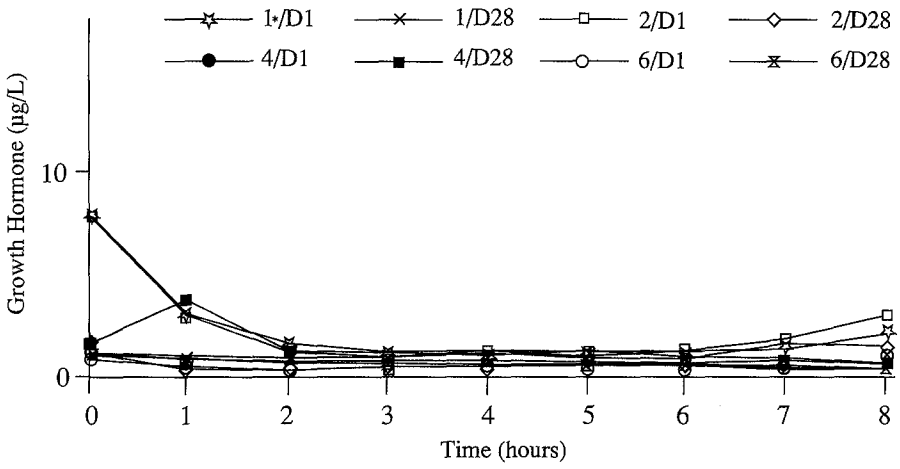

Fig 2. The 8-hour GH serum concentrations on days 1 and 28 after injections no. 1, 2, 4, and 6 of either a 20- or 30-mg dose of Sandostatin® LAR® in an illustrative patient.

4, which shows the 8-hour mean (and 95% confidence intervals) of the GH serum concentrations, on day 28 after each injection during the first 6-month extension study in patients treated with either 20 or 30 mg Sandostatin® LAR® at 4-week intervals. The 20-mg dose of Sandostatin® LAR®, administered at 4-week intervals, which delivered average octreotide concentrations of 1,348 ± 483 ng/L in steady-state conditions (Fig 5), provided adequate control of patients who had been well controlled during treatment with the 0.1-mg thrice-daily dose of SC Sandostatin®. The 30-mg dose of Sandostatin® LAR®, administered at 4-week intervals releasing octreotide at average concentrations of 2,631 ± 1,026 ng/L, also provided adequate control in patients previously treated with 0.2 mg SC Sandostatin® thrice daily. However, suppression of GH serum concentrations to less than 5 µg, 2 µg, and even 1 µg/L was recorded in more patients and more consistently during long-term treatment with Sandostatin® LAR® than during SC Sandostatin® treatment, as shown in Table 1.

A marked decrease in IGF-1 serum concentrations and

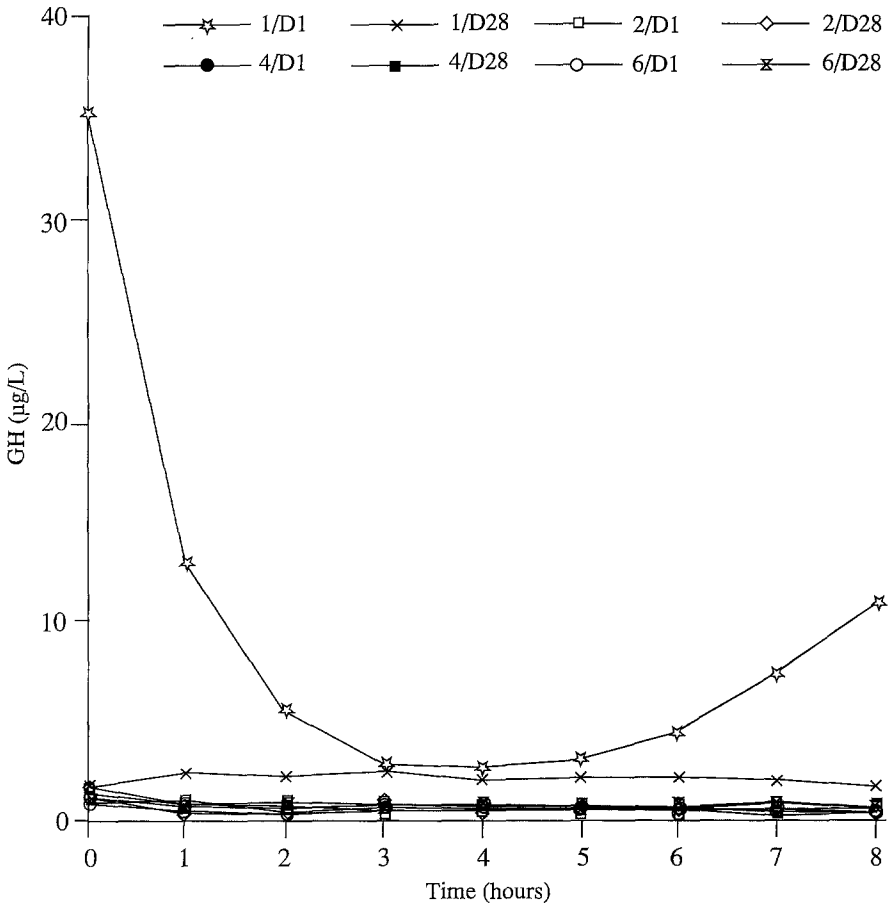

Fig 3. The 8-hour GH serum concentrations on days 1 and 28 after injections no. 1, 2, 4, and 6 of the 30-mg dose of Sandostatin® LAR® in an illustrative patient.

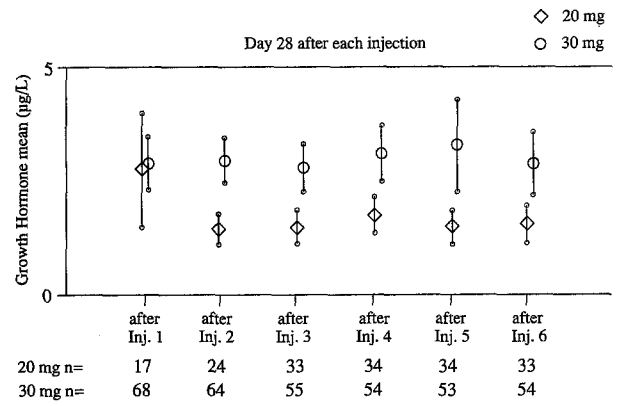

Fig 4. Mean (and 95% confidence interval [CI]) of the 8-hour GH serum concentrations on day 28 after consecutive injections in patients treated with either a 20- or 30-mg dose of Sandostatin® LAR® at 4-week intervals.

normalization of IGF-1 concentrations was observed after the first double-blind 10-, 20-, or 30-mg dose of Sandostatin® LAR®. Even better suppression was recorded during long-term treatment, as shown in Table 2. In addition to the progressive decrease/normalization of total serum concentration of IGF-1, a marked suppression of the fasting serum concentration of free IGF-1 and a significant increase in IGF-binding protein-1 was observed.[2,3]

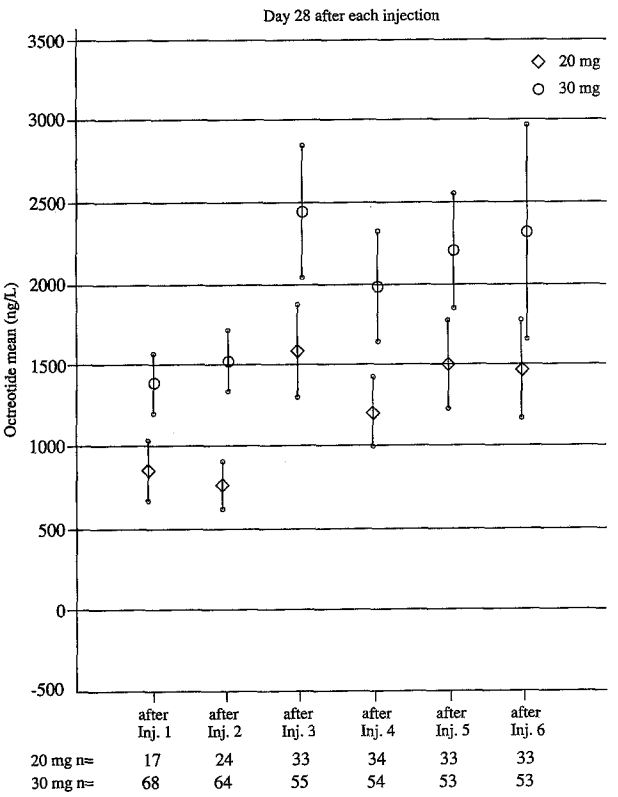

Fig 5. Mean (and 95% CI) of the 8-hour octreotide serum concentrations on day 28 after consecutive injections in patients treated with either a 20- or 30-mg dose of Sandostatin® LAR® at 4-week intervals.

Table 1. Categorical Analyses of Suppression of GH Secretion During SC Sandostatin® Treatment and (a) After the First Double-Blind Injection of Sandostatin® LAR® and (b) After Long-Term Open Treatment (up to the 19th injection) With Sandostatin® LAR®

	GH Concentrations		
	<5 µg/L	<2 µg/L	<1 µg/L
(a) During steady-state SC treatment (0.1-0.2 mg thrice daily) After the 1st injection of 10, 20, or 30 mg Sandostatin® LAR®	77/93 (82.8%)	37/93 (39.8%)	9/93 (9.7%)
	80/93 (86%)	52/93 (55.9%)	15/93 (16.1%)
(b) During steady-state SC treatment (0.1-0.2 mg thrice daily) After the last injection in long-term treatment with Sandostatin® LAR®	83/101 (82.2%)	39/101 (38.6%)	10/101 (9.9%)
	95/101 (94.1%)	55/101 (54.6%)	24/101 (23.8%)

In parallel with normalization of the GH and IGF-1 serum concentrations, a marked clinical improvement was recorded in most patients, as shown in Table 3. Disappearance of symptoms/signs was already noted at the end of the first open extension study after a total of seven injections of Sandostatin® LAR®. Furthermore, a sustained clinical improvement was noted during the extension of the open studies (with up to 19 injections), with 36 of 101 patients (35.6%) becoming asymptomatic.

A shrinkage of the GH-secreting adenoma by greater than 20% was also recorded in 12 of 14 patients treated with Sandostatin® LAR® after receiving only 2 to 4 weeks of treatment with SC Sandostatin® and in 11 of 18 patients receiving Sandostatin® LAR® as adjuvant therapy after failure of surgery.

The systemic tolerability of Sandostatin® LAR® was

Table 2. Suppression of IGF-1 Serum Concentrations to Within the Normal Range, During SC Sandostatin® Treatment and (a) After the First and Seventh Injections of Sandostatin® LAR® in All Patients Entered in the Double-Blind Studies and Their First 6-Month Extension and (b) in the Whole Group of 101 Patients Treated Long-Term in Open-Label Studies With Sandostatin® LAR®

(a) During treatment with Sandostatin® SC (0.1-0.2 mg thrice daily) After the 1st injection of Sandostatin® LAR®	44/93 (47.3%) patients
	46/93 (49.5%) patients
After the 7th injection of Sandostatin® LAR® (individual doses)	49/89 (55.1%) patients
(b) During treatment with Sandostatin® SC (0.1-0.2 mg thrice daily) After the last injection of Sandostatin® LAR®	46/101 (49.5%) patients
	66/101 (65.3%) patients

Table 3. Disappearance of Symptoms/Signs of Acromegaly After the Seventh Injection of Sandostatin® LAR® in Patients Who Presented the Symptoms/Signs

Symptom Resolved	No. of Patients
Carpal tunnel syndrome	30/37 (81.1%)
Paresthesias	36/46 (78.3%)
Excessive perspiration	31/53 (58.5%)
Joint pains	33/62 (53.2%)
Headache	28/59 (47.5%)
Fatigue	31/66 (47.0%)

good, with the following adverse events recorded in the 93 patients treated with doses of 10, 20, or 30 mg of Sandostatin® LAR® in the single-dose, double-blind studies: episodic abdominal pain, 30 of 93 (32%) patients; diarrhea, 42 of 93 (45%); flatulence, 33 of 93 (35%); steatorrhoeic stools, nine of 93 (10%); nausea, nine of 93 (10%); vomiting, seven of 93 (8%); and hair loss eight of 93 (9%). Most adverse events were mild and short term (1 to 2 days). The prevalence of adverse events decreased markedly and progressively during extension of the treatment. After the seventh injection of Sandostatin® LAR®, episodic abdominal pain was reported by three of 101 patients (3%), flatulence by eight of 101 (8%), loose stools by 11 of 101 (11%), nausea by one of 101 (1%), single episode of vomiting by one of 101 (1%), and hair loss by eight of 101 (8%). No significant difference between the incidence of adverse events in patients treated with 20- or 30-mg doses was detected using Fisher's exact test. The tolerability of the 40-mg dose was also good in all patients treated with this dose in the attempt to obtain the best suppression of GH and IGF-1 serum concentrations. The local tolerability at the injection site was good, with only a few patients reporting sporadic mild/moderate, short-term pain on the day of injections. No impairment in safety tests was noted, except for a transitory anemia, recorded after 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 eight of 101 patients with diabetes mellitus at entry, one patient improved markedly, three showed a slight worsening, and the others did not show any relevant changes during the whole observation period. The evaluation of thyrotropin, total and free thyroxine, and triidothyronine serum concentrations did not reveal any impairment of thyroid function during treatment with Sandostatin® LAR®.

Repeated echographic examination of the gallbladder region showed the following newly occurring abnormalities after up to 30 months of treatment: asymptomatic gallstone in four of 101 patients, microlithiasis in four of 101, sediment in nine of 101, sludge in five of 101 patients, biliary duct dilatation in two of 101, and gallbladder dilatation in two of 101 patients.

CONCLUSIONS

Sandostatin® LAR® administered as single IM injections, given at 4-week intervals, increases the acceptability of long-term therapy in acromegalics. In addition, by releasing stable concentrations of serum octreotide and by sustained suppression of GH secretion, Sandostatin® LAR® appears to be as effective as SC infusions of Sandostatin® and at least as effective as the intermittent SC administration. Indeed, in the patients switched from SC treatment to Sandostatin® LAR®, suppression of GH secretion and serum IGF-1 concentrations and clinical improvement have been either as good as or better than with Sandostatin® SC. A larger number of patients showed suppression of GH serum concentrations to less than 2 μg/L, normalization of serum IGF-1 concentrations, and clinical improvement. In addition to the improvement of symptoms/signs of acromegaly seen in most patients, some patients have become asymptomatic. Since the drug is well tolerated, patients can be safely switched from SC Sandostatin® to Sandostatin® LAR® treatment, starting at a dose of 20 mg IM administered at 4-week intervals. The dose can be increased to 30 mg at 4-week intervals in patients in whom the suppression of GH and IGF-1 is not considered satisfactory after the first three injections of 20 mg Sandostatin® LAR®.

Thus, due to its excellent efficacy, good tolerability, convenience of administration, and acceptability by patients, Sandostatin® LAR® can be considered the medical treatment of choice in acromegalic patients.

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