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Sandostatin LAR in acromegaly: a 6-week injection interval suppresses GH secretion as effectively as a 4-week interval

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SUMMARY

INTRODUCTION: Depot preparations of long-acting somatostatin analogues are being used increasingly in the treatment of GH hypersecretion in patients with acromegaly, either as primary treatment or as secondary treatment following incomplete surgery. In 60% of these patients, Sandostatin long-acting release (LAR), the depot preparation of octreotide, achieves effective suppression of serum GH (< 5 mU/l) and IGF-I levels. The advice is to administer Sandostatin LAR at 4-week intervals. After injection, serum octreotide shows an initial peak and thereafter maximal values between 14 and 42 days. There have been suggestions that the dose interval of this preparation could be increased, resulting in reduced costs, although this concept has not been confirmed by studies.

AIM OF THE STUDY: We performed a prospective, cohort study in patients with active acromegaly but with normal serum GH and IGF-I levels during Sandostatin LAR treatment to assess whether the dose interval could be safely increased from 4 to 6 weeks, without significant effect on serum GH concentrations or other biochemical and clinical markers of GH hypersecretion.

PATIENTS AND METHODS: Fourteen patients (seven males) with GH concentrations below 5 mU/l during Sandostatin LAR treatment entered an 8-week withdrawal study following an injection. Subsequently, during an interval study patients received injections at 6-week intervals (t = 0, 8, 14, 20, 26, 32, 38 and 44 weeks). Study parameters (fasting GH, average GH of eight plasma samples, IGF-I, and octreotide concentrations, symptoms score and quality-of-life score) were assessed 2, 4, 6 and 8 weeks following the first injection (withdrawal) and at 26 and 44 weeks (interval study) before the next injection.

RESULTS: During the withdrawal study, mean serum GH concentration increased significantly from 1.68 ± 0.3 at 4 weeks to 2.57 ± 0.5 mU/l at 6 weeks ($P = 0.04$, 4 vs. 6 weeks) and to 2.89 ± 0.4 mU/l at 8 weeks ($P < 0.001$, 4 vs. 8 weeks). Mean serum GH concentration was below 5 mU/l in all patients at all time points, except for one patient at 8 weeks, and IGF-I levels remained normal in all patients. During withdrawal up to 8 weeks there was no significant change in serum IGF-I concentration, symptoms score or quality-of-life score. Mean serum octreotide decreased significantly from 1610 ± 355 ng/l at 2 weeks to 1045 ± 272 ng/l at 6 weeks ($P = 0.002$, 2 and 4 vs. 6 weeks) and to 559 ± 147 ng/l at 8 weeks.

In the interval study, one patient had mean serum GH above 5 mU/l associated with an increase in symptoms at 26 weeks and she was withdrawn from the study. The remaining 13 patients completed the 6-weekly injection study protocol and in the long term no significant changes in mean serum GH concentration, IGF-I concentration or symptom scores were observed (6 vs. 26 and 44 weeks). All patients had a mean serum GH concentration < 5 mU/l and serum IGF-I remained normal in 11 out of 14 patients at 26 weeks and nine out of 13 patients at 44 weeks. Moreover, the mean octreotide concentrations measured 6 weeks after a Sandostatin LAR injection did not decrease in the long term.

CONCLUSION: On the basis of serum GH concentrations, most patients with serum GH levels < 5 mU/l during Sandostatin LAR treatment using a 4-weekly schedule can be effectively treated with 6-weekly injections. However, during long-term treatment with 6-weekly injections, discordant IGF-I and GH results were observed in 30% of the patients and careful clinical monitoring is therefore required.

INTRODUCTION

Acromegaly, caused by a GH-producing adenoma in the pituitary, is associated with considerable morbidity and a two- to threefold increase in mortality, which can be reduced when serum GH and IGF-I concentrations are effectively reduced by treatment (1,2). The first-line treatment, transsphenoidal microsurgery, reduces serum GH concentration in almost all patients. Strict normalization of serum GH concentration (< 5 mU/l), glucose-suppressed serum GH concentration and IGF-I concentration is achieved in 60–70% of patients, when surgery is performed by an experienced pituitary surgeon (3,4). For patients with persistent or recurrent GH hypersecretion other modes of treatment include radiotherapy and GH suppressive treatment with somatostatin analogues. After radiotherapy, serum GH concentration gradually decreases and normalization of serum GH and IGF-I concentrations occurs after many years, with the associated loss of anterior pituitary function in more than 50% of patients (5,6,7). Since the introduction of the long-acting somatostatin analogue octreotide, which effectively suppresses serum GH and IGF-I concentrations in 40–60% of patients (8–11), pituitary irradiation is reserved generally for patients with insufficient response to medical therapy or side-effects to medical treatment.

To date there have been 3 years of clinical experience with the depot preparation of octreotide, Sandostatin long-acting release (LAR). Besides the convenience of this 1-monthly intramuscularly injected depot preparation, there is the same or even increased effectiveness of the depot preparation compared to three daily subcutaneous injections in lowering serum GH (12,13). Increasing the dose of Sandostatin LAR from 20 mg to 30 mg in dose-finding studies achieves normalization of IGF-I or GH concentrations in an additional number of patients not controlled on the lower dose (14). The advised dose interval is 28 days and although there have been suggestions from short-term withdrawal studies that the interval could possibly be prolonged (15,16), there are no clinical data on the variation of dosage interval of Sandostatin LAR therapy. Octreotide therapy is expensive and the associated costs would be reduced considerably if a schedule with less frequent injections was equally effective in suppressing GH levels.

The present study was performed to validate the hypothesis that the dose interval of Sandostatin LAR injections can be safely increased to 6 weeks in those patients sensitive to octreotide who attain normal serum GH levels with 20 mg Sandostatin LAR therapy every 4 weeks.

PATIENTS AND METHODS

Patients

Patients with acromegaly using Sandostatin LAR for at least 3 months were selected from our pituitary database, which has previously been described in detail (4,6,7). Patients were eli-

Table 1. Clinical and biochemical characteristics of the patients

Patient ¹	Age (years)	Transsphenoidal surgery ²	Irradiation (40 Gy) ²	Duration of Sandostatin LAR treatment (months)	Sandostatin LAR (mg)	Mean GH(mU/L) ³	IGF-1 (nmol/L) ³	IGF SD score
F1	50	Y, 1986	N	24	20	2.43	19	0.14
F2	73	N	N	7	10	2.01	18	0.62
F3	63	Y, 1990	N	24	20	0.83	12	-0.58
F4	51	Y, 1982	Y, 1983	36	20	2.50	14	-0.82
F5	36	Y, 1983	Y, 1996	24	20	3.98	14	-1.59
F6	68	N	N	11	20	1.34	14	-0.08
F7	55	N	N	24	20	1.60	23	0.92
M1	70	Y, 1972	Y, 1970	18	20	1.87	16	0.22
M2	54	Y, 1988	N	24	20	0.49	20	0.34
M3	61	Y, 1986	N	24	20	1.29	24	1.83
M4	41	Y, 1995	Y, 1996	7	20	2.71	13	-1.01
M5	57	Y, 1993	N	24	20	0.95	18	-0.05
M6	77	Y, 1982	N	24	20	0.68	14	-0.18
M7	60	Y, 1977/1996	N	24	20	0.37	15	0.02

¹ F=female, M=male.

² Y= yes, N=no, one patient underwent transsphenoidal surgery twice(M7).

³ GH and IGF-I levels measured 2 weeks after Sandostatin LAR injection in the withdrawal study (t=2 weeks).

gible for entering the study protocol if they had random serum GH concentrations < 5 mU/l and a normal IGF-I during Sandostatin LAR treatment at a 4-weekly scheme and at a dose of 10, 20 or 30 mg. Twenty-eight patients were on chronic treatment with Sandostatin LAR. Six of them could not participate in the present study because of concomitant disease (including malignancies and major vascular disease) and eight had serum GH concentrations above 5 mU/l. Thirteen patients were well controlled with Sandostatin LAR 20 mg and one patient with 10 mg. Characteristics of these 14 included patients are detailed in Table 1.

Study protocol

We studied the patients in a prospective, cohort study in the following two protocols.

Withdrawal study (weeks 0–8)

To assess the effects of short-term withdrawal of octreotide, the study parameters were measured 2, 4, 6 and 8 weeks after a regular Sandostatin LAR injection (t = 0 weeks). The study baseline was between March and August 2000.

Six-week interval study (weeks 8–44)

All 14 patients entered the 6-week interval regimen study after the withdrawal study and were tested 6 weeks after the third injection at a 6-week interval just before the following injection ($t = 26$ weeks). Patients with serum GH concentrations < 5 mU/l at $t = 26$ weeks (13 out of 14 patients) continued on a 6-week interval schedule for another 18 weeks. Study parameters were evaluated at the end of this period ($t = 44$ weeks). The protocol was approved by the Ethics Committee of the Leiden University Medical Centre and all patients gave written informed consent.

Study parameters

After an overnight fast, patients were assessed in the outpatients clinic of the Department of Endocrinology. An indwelling intravenous catheter was inserted in a forearm vein from which all blood samples were collected. The first fasting blood sample taken was assessed for serum GH, IGF-I and octreotide concentrations. Thereafter, the patients were allowed to eat and drink, and seven blood samples were drawn every 30 min and assessed for serum GH concentration. Mean GH was calculated from eight consecutive samples.

A well-established self-rating quality-of-life questionnaire, The Nottingham Health Profile (17,18), and an acromegaly specific symptom score were used to assess whether the withdrawal of Sandostatin LAR influenced clinical features of acromegaly. The following symptoms were assessed for presence or absence and for severity (score 0–4): paraesthesias, fatigue, osteoarthralgia, headache and perspiration. The sum of all symptoms was measured at all study visits, similar to previous clinical trials evaluating Sandostatin LAR treatment (19–21).

Assays

Serum GH was measured with an immunofluorometric assay specific for the 22-kDa GH protein (Wallac, Turku, Finland). Human biosynthetic GH was used as a standard, calibrated against WHO-IRP 80-505. For conversion from mU/l to $\mu\text{g/l}$ divide by 2.6. The detection limit was 0.03 mU/l and the interassay coefficient of variation (CV) 1.6–8.4% between 0.25 and 40 mU/l. We considered $\text{GH} < 5$ mU/l (equivalent to 1.9 $\mu\text{g/l}$) as adequate suppression during medical therapy.

The total serum IGF-I concentration was determined by radioimmunoassay (RIA) after extraction and purification on ODS-silica columns (Incstar Corp., Stillwater, MN, USA). The interassay CV was less than 11%. The detection limit was 1.5 nmol/l. Age-related normal data were determined in the same laboratory. IGF-I was also expressed as an SD-score from age-related normal levels. Serum octreotide was determined with an RIA. The limit of detection was 50 ng/l. The intra-assay CV was 6–10%. The measurements were performed in the research laboratory of Novartis (Basel, Switzerland).

Injections

Sandostatin LAR injections were given by the patients' general practitioners, who were experienced in giving these injections, or at the endocrinological ward in our hospital at the beginning of the withdrawal study ($t = 0$ weeks) and at 8, 14, 20 weeks and 26, 32, 38 weeks during the 6-week interval protocol.

Statistical analysis

Data are expressed as mean \pm SEM unless mentioned otherwise. Statistics (ANOVA for repeated measures and descriptive statistics) were calculated using Systat version 10.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Baseline characteristics

Patients and treatment characteristics are detailed in Table 1. Seven males and seven females with a mean age of 58.3 years participated in the study. Three patients received Sandostatin LAR as primary treatment. The remaining 11 patients had undergone pituitary surgery, in four patients combined with postoperative radiotherapy 4–30 years before entering the study. Sandostatin LAR treatment was started after incomplete surgery in seven patients and for late postoperative recurrence in four patients. All patients used Sandostatin LAR for at least 3 months before entering the present study (range 3–24 months).

All patients entered the withdrawal study and completed the 6-week protocol with evaluation at 26 weeks. One patient (F1) was withdrawn from the study at 26 weeks because of an increase in mean GH concentration above 5 mU/l and clinical symptoms, the other patients continued with the 6-weekly injection interval study until 44 weeks.

Withdrawal study

Withdrawal of Sandostatin LAR for 8 weeks resulted in a significant increase in both mean and fasting serum GH concentrations ($P < 0.001$ and 0.03 , respectively) (Fig. 1a,b). Mean GH concentration increased from 1.68 ± 0.3 mU/l at 4 weeks to 2.57 ± 0.5 mU/l at 6 weeks ($P = 0.03$, 4 vs. 6 weeks) and 2.89 ± 0.4 mU/l at 8 weeks ($P < 0.001$, 4 vs. 8 weeks) after the Sandostatin LAR injection. Mean serum GH concentration was below 5 mU/l in all patients at all time points, except in one patient at 6 weeks, due to a GH peak during the sampling procedure (patient M4, GH 7.6 mU/l, see Table 1) followed by a mean GH of 3.9 mU/l at 8 weeks, and another patient who had elevated mean serum GH at 8 weeks (F1, GH 6.8 mU/l). Fasting serum GH remained suppressed (< 5 mU/l) in all patients except one (M4), who had a fasting GH at 6 weeks of 5.3 mU/l but a fasting GH concentration of 4.6 mU/l at 8 weeks.

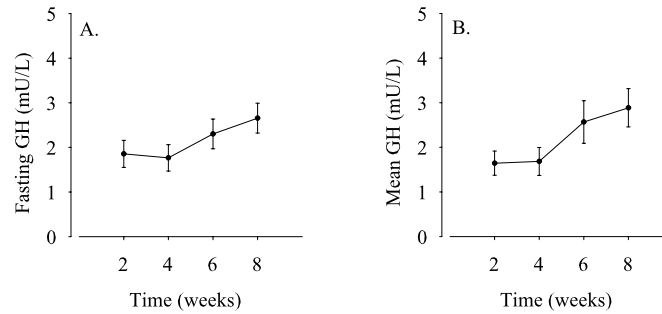


Figure 1. (a) Fasting and (b) mean serum GH concentration 2, 4, 6 and 8 weeks following Sandostatin LAR injection.

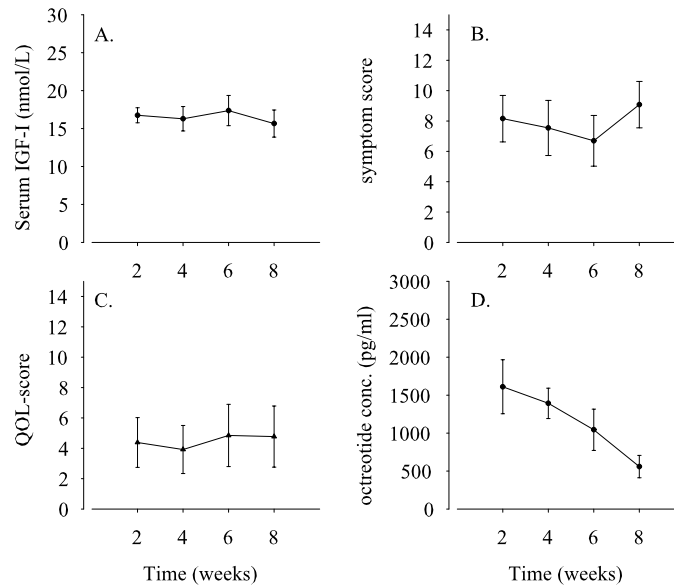


Figure 2. Study parameters measured during the withdrawal study 2, 4, 6 and 8 weeks following a Sandostatin LAR injection: (a) IGF-I concentration; (b) symptom score; (c) quality-of-life score; (d) octreotide concentration.

There was no significant increase in IGF-I concentration during the withdrawal study. IGF-I at 2 weeks was 16.5 ± 1.6 nmol/L, at 6 weeks 17.5 ± 2.0 nmol/L and at 8 weeks 15.5 ± 1.8 nmol/L ($P = 0.88$, Fig. 2a). Serum IGF-I concentrations remained normal in all patients at 6 and 8 weeks during the withdrawal study. Corresponding mean IGF-I SD-scores were -0.02 ± 0.2 2 weeks after the injection, -0.11 ± 0.2 at 4 weeks, 0.09 ± 0.6 at 6 weeks and -0.2 ± 0.2 at 8 weeks. Both quality-of-life and symptom scores did not change during the withdrawal study (data not shown). As expected, the mean serum octreotide concentration decreased significantly ($P = 0.001$) during the withdrawal study from 1610 ± 55 ng/ml at 2 weeks to 1092 ± 201 ng/ml at 4 weeks, 1005 ± 202 ng/ml at 6 weeks ($P = 0.002$, 2 and 4 vs. 6 weeks) and 559 ± 100 ng/ml at 8 weeks (Fig. 2d).

Table 2. Individual data of serum mean GH concentration and serum IGF-I levels including age-related SD score of 14 patients in the withdrawal and interval study.

Patient	Mean GH conc. (mU/L)				IGF-I conc. (nmol/L)/age-related SD score			
	4 wks	6wks	26 wks	44 wks	4 wks	6wks	26 wks	44 wks
F1	4.39	3.91	5.49	¹	16 / -0.4	22 / 0.7	24 / 1.1	¹
F2	2.59	3.27	2.64	2.49	10 / -1.0	7.5 / -1.5	15 / 0.0	12 / -0.6
F3	0.83	2.12	0.82	1.21	14 / -0.2	24 / 1.8	15 / 0.0	15 / 0.0
F4	2.61	2.77	2.76	3.42	19 / 0.1	12 / -1.2	12 / -1.2	9.9 / -1.6
F5	3.39	4.10	3.27	3.1	9.1 / -2.5	34 / 2.0	18 / 0.9	12 / -2.0
F6	0.94	1.50	1.25	1.31	20 / 1.0	16 / 0.2	21 / 1.2	23 / 1.8
F7	1.24	1.89	4.11	2.04	32 / 2.6	9.1 / -1.8	16 / -0.4	35 / 3.2
M1	1.38	1.30	2.06	1.32	19 / 0.8	13 / -0.4	18 / 0.6	11 / -0.8
M2	0.86	1.43	1.55	0.44	14 / -0.8	18 / -0.1	17 / -0.2	24 / 1.1
M3	1.14	1.51	1.25	1.93	18 / 0.6	21 / 1.2	32 / 3.4	33 / 3.6
M4	2.12	7.64	3.63	3.64	11 / -1.4	7.8 / -2.0	34 / 3.0	33 / 2.8
M5	1.15	2.61	1.20	1.32	21 / 0.5	22 / 0.7	53 / 4.0	37 / 3.6
M6	0.50	0.97	0.62	0.42	9.9 / -1.0	23 / 1.6	13 / -0.4	22 / 1.4
M7	0.45	0.93	1.47	1.25	15 / 0.0	14 / -0.2	25 / 2.0	19 / 0.8

¹ F1 was withdrawn from the study because of clinical symptoms at 26 weeks.

Six-week interval study

Mean serum GH concentration in the 14 patients did not increase significantly from week 6 to week 26 (i.e. 2.57 ± 0.48 and 2.29 ± 0.38 mU/l, respectively, $P = 0.49$). Moreover, neither fasting GH, IGF-I and octreotide concentrations nor the quality-of-life and symptom scores changed significantly from 6 to 26 weeks. Individual data are detailed in Table 2. At 26 weeks, only one patient (F1) had a mean GH above 5 mU/l together with an increase in acromegalic symptoms. She was withdrawn from the study at 26 weeks and continued with a (regular) 4-week injection interval.

The other 13 patients completed the 6-weekly injection study and were studied at 26 weeks and 44 weeks (see Table 3). No significant increase was observed in serum GH or IGF-I levels in follow-up. None of the patients had elevation of the mean serum GH concentration above 5 mU/l and there was no increase in symptom score or quality-of-life questionnaire score. However, three out of 14 patients at 26 weeks and four out of 13 patients at 44 weeks had elevated serum IGF-I concentration. Mean serum octreotide level did not significantly change comparing levels between 6 weeks and 26 or 44 weeks (see Table 3).

Table 3. Study parameters of 13 patients treated with Sandostatin LAR at 6-week injection intervals

	6 weeks	26 weeks	44 weeks	P (ANOVA)
Fasting GH (mU/L)	2.36 ± 0.36	2.08 ± 0.45	1.91 ± 0.29	0.414
Mean serum GH (mU/L)	2.47 ± 0.50	2.05 ± 0.31	1.84 ± 0.29	0.161
IGF-I (nmol/L)	17 ± 2.2	22.2 ± 3.2	22.1 ± 2.7	0.218
IGF-1 SD score	0.09 ± 0.36	1.07 ± 0.57	1.04 ± 0.54	0.198
QOL	5 ± 2.0	4 ± 1.4	4 ± 1.3	0.560
Symptom score	7 ± 1.7	7 ± 1.3	7 ± 1.3	0.916
Serum octreotide concentration (ng/L)	995 ± 290	680 ± 105	755 ± 130	0.614

QOL, quality of life. Data shown are mean ± SEM of 13 patients who completed the long-term interval study.

DISCUSSION

In this prospective cohort study we showed that most patients with normal serum GH levels during a 4-weekly Sandostatin LAR injection schedule also had normal GH levels during a 6-weekly schedule. A 6-weekly schedule was also associated with the absence of acromegalic symptoms or decreased quality of life in 13 out of 14 patients. However, in discrepancy with the normal mean serum GH levels and unchanged acromegalic symptoms scores during the 6-weekly scheme, four patients showed an increase in serum IGF-I levels above age-related normal values.

This is the first study assessing the short- and longer-term effects of a 6-week dosage interval of Sandostatin LAR on clinical and biochemical parameters of GH (hyper)secretion, although others have suggested that one injection of Sandostatin LAR might effectively suppress serum GH for a period longer than 4 weeks (15). In their study, Jenkins and colleagues measured serum GH levels 6 weeks after the first injection of Sandostatin LAR in patients previously treated with subcutaneous octreotide and showed effective suppression up to 6 weeks after a single injection. (22) studied serum GH, IGF-I levels and symptoms during withdrawal of Sandostatin LAR up to 16 weeks. They observed no difference between 4 and 8 weeks after an injection, but a significant rise in GH concentration 12 and 16 weeks after a Sandostatin LAR injection, suggesting an ongoing effect of Sandostatin up to 12 weeks. In the same study, serum IGF-I concentration was significantly elevated only after 8 weeks, but the symptom score did not change until 16 weeks (22). The present study confirms the results regarding the unchanged symptom scores.

Active acromegaly is associated with increased morbidity and mortality. Several retrospective studies have demonstrated that GH levels below 5 mU/l are associated with normalization of life expectancy (2,23–25). One study investigating mortality in relation to IGF-I (1) showed this to be normalized with a normal serum IGF-I concentration. IGF-I is used as biochemical marker of disease activity and a recent consensus statement advises the use of both IGF-I and (glucose-suppressed) GH measurements (26). For medically treated patients

with active acromegaly, adequate GH suppression should be accompanied by normal IGF-I concentrations. Discordant results of GH and IGF-I may occur in up to 30% of patients (27,28), as observed in some of our patients during the 6-week interval schedule. It is unknown which criterion is the most important predictor for morbidity and mortality in these patients, and although the reduced mortality risk is proven more strongly for a serum GH < 5 mU/l and there was no increase in clinical symptoms in these patients, we believe that the criterion of GH suppression to below 5 mU/l may not be sufficient. Considering the increased IGF-I levels and taking into account the study of Swearingen et al. (1), three patients with discrepant GH and IGF-I results were therefore advised to resume the previous 4-weekly injection interval and one patient was switched to another long-acting somatostatin analogue after completion of the study.

The pharmacodynamical profile of a single Sandostatin LAR injection with a concentration plateau between 14 days and 42 days, a gradual decrease of octreotide levels thereafter and detectable levels up to 60 days (29,30) supports the concept of increasing the dosage interval. After three injections at a 4-weekly interval a steady state is reached with an octreotide level 1.6 times higher than after a single injection (31). In the present study we measured a significant decrease in octreotide levels from 2 to 8 weeks and undetectable levels were found in three out of 14 patients at 8 weeks. There was, however, no significant decrease in octreotide levels in our patients between 6, 26 and 44 weeks. This suggests the presence of a new steady state, in accordance with unchanged serum GH levels. Mean octreotide levels were 678 ± 105 and 754 ± 133 ng/l at 26 and 44 weeks, respectively, and indeed, serum octreotide concentrations above 600 ng/l are reported to be therapeutic (12).

In acromegalic patients treated primarily or after incomplete surgery with GH suppressive medication, the cost of life-long treatment with a somatostatin analogue is considerable, in the range of 10 000 euro per year. This study confirms the long-term efficacy of a 6-weekly Sandostatin LAR injection schedule in patients sensitive to octreotide, which establishes a 33% cost reduction and also increases convenience for the patient (less-frequent injections). Another option to achieve cost reduction in well-controlled patients, not assessed to date, is to reduce Sandostatin LAR dose instead of increasing the dosage interval. We believe that our protocol is more convenient for patients because of the reduced number of injections.

Another available somatostatin analogue depot preparation, Lanreotide SR, suppresses serum GH and IGF-I concentrations as effectively as subcutaneous octreotide, when injected at 10–14-day intervals (32–34). Comparison of Octreotide LAR and Lanreotide SR showed a slightly better efficacy of Sandostatin LAR (14,35,36). As Lanreotide SR has a different release pattern than Sandostatin LAR, we cannot elaborate on the potential effects of increasing dosage interval of this depot preparation. However, others have performed withdrawal studies in Lanreotide SR, showing individual variability in response and also potential dosage interval increments in short-term studies (15,37).

Patients with acromegaly requiring GH suppressive medication are heterogeneous and have different basal GH levels and sensitivity to octreotide. Therefore, the dosage and interval of Sandostatin LAR injections remains to be individually adjusted. Both serum GH and IGF-I concentrations are important in this evaluation and, as also shown in this study, discrepant results may be present. The development of more potent somatostatin analogues, aimed at different somatostatin receptor subtypes, and GH receptor blocking agents is encouraging for patients insufficiently sensitive to octreotide. The GH receptor antagonist Pegvisomant is an effective and safe treatment for acromegaly with follow-up up to 18 months (38,39). In vitro studies with BIM 23244, a somatostatin subtype 2 and 5 selective analogue suggests enhanced GH suppression in adenomas resistant to octreotide (40).

In conclusion, long-term treatment with Sandostatin LAR at a 6-weekly injection interval effectively suppresses serum GH in 13 out of 14 patients and IGF-I levels in 70% of the patients previously well controlled with a 4-weekly scheme. Therefore, we suggest an attempt to increase the dose interval from 4 to 6 weeks in patients well controlled with a 4-weekly schedule.

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