non-endocrine systems (TSH, perhaps PRL and gonadotropins, pancreatic and gastrointestinal hormones, growth factors, gastrointestinal exocrine secretions, etc.) (14, 15) that cause several effects, not necessarily untoward, needing further investigation.

This multicenter octreotide study had the following aims: to ascertain the percentage of patients in whom octreotide is able to reduce serum GH levels to less than 2.5 μg/l, clarifying the influence of previous therapy and other possible prognostic factors on drug responsiveness; to evaluate the octreotide effects on GH abnormal responses; and to study octreotide effects on PRL secretion and thyroid function.

With respect to previous trials, particular attention was paid to the study of patients not previously submitted to pituitary radiotherapy, because irradiation may affect GH secretion and decrease tumoral mass for as long as 10 or more years. In addition, because diabetes mellitus, hypertension and dyslipidemia are all more frequent in acromegalic patients than in the general population and can worsen morbidity and mortality, the effects of octreotide therapy on these conditions were investigated.

Patients and methods

A prospective, open label study was performed in 10 Italian centers after having being approved by the local ethic committees. All the patients participating in the study gave their informed written consent.

Patients

Sixty-eight acromegalic patients (43 women and 25 men) 19–70 years old (mean ± SD = 45.9 ± 12 years) were included in the study. All had clinically active acromegaly documented by serum GH levels not suppressible below 2 μg/l after the oral glucose tolerance test (OGTT) and elevated insulin like growth factor I (IGF-I) levels.

Twenty patients had not been treated previously, 10 had received only medical treatment with dopaminergic drugs and 38 had been submitted to unsuccessful neurosurgical removal of the GH-secreting adenoma. Ten patients were given postoperative radiotherapy (40–60 Gy) followed by bromocriptine administration 3 months to 15 years (median: 3 years and 6 months) before entering the study, while other 16 patients postoperatively received bromocriptine therapy that was discontinued at least 1 month prior to the start of the study.

Typical signs of acromegaly were present in all patients. With regard to concomitant endocrine diseases, 16 patients (24%) had diabetes mellitus, one had (1.5%) hyperthyroidism, four (6%) had hypothyroidism, two (3%) had adrenal failure and 51 (75%) had goiter. Visual field examination was abnormal in 16 (23%) of the patients. All patients underwent neuroradiological imaging of the hypothalamic–pituitary region: 48 by computed tomography (CT) scan, nine by magnetic resonance (MR) and 11 by both CT scan and MR. Forty-one examinations (60%) were indicative of the presence of a pituitary adenoma (14 microadenomas and 27 macroadenomas). Among the 27 patients with no radiological evidence of pituitary tumor, 20 were previously operated on and three showed an empty sella. It is likely that in the four remaining patients the tumor was too small to be detected.

Protocol

Octreotide was administered subcutaneously at a dose of 100 μg t.i.d. for 1 year. Compliance was monitored by comparing the number of vials dispensed with those returned. Doses could be adjusted to reduce side effects or to improve hormonal responses: owing to gastrointestinal side effects, the daily doses were reduced to 100–200 μg in six patients temporarily (2 weeks), in one case during the whole study period and in four after the 4th month of therapy. A temporary increase of the dose and frequency of injections to 100 μg q.i.d. was performed in one case from the 5th to the 7th month for relieving severe headache. Because of insufficient hormonal response, the dose was increased after the 4th month in 11 patients (to 400 μg in three cases, to 450 μg in four cases and to 600 μg per day in another four cases).

Pretreatment studies included the following tests: an 8-h saline infusion, with a light, standardized meal given at 4 h; a 4-h OGTT (75 g orally); a TRH test (200 μg iv); and a GnRH test (100 μg iv). During octreotide treatment, the patients were studied every 3 months. At 3 and 12 months an 8-h saline infusion, with octreotide injection given at time zero, was performed. The OGTT was repeated after 6 months of therapy and the TRH and GnRH tests were repeated after 9 months. The OGTT, TRH and GnRH tests were administered 2 h after the morning octreotide injection. Blood was drawn: during saline infusion every hour for serum GH measurement and every 30–60 minutes for glucose and insulin assay; after glucose load every 30 min for serum GH, insulin and glucose determinations; during the TRH test at 0, 20, 30, 60, 120 and 180 min for GH, PRL, TSH, free T_3 (fT_3) and free T_4 (fT_4) measurements; and during the GnRH test at 0, 20, 30 and 60 min for GH evaluation. Additionally, serum levels of IGF-1, free T_3, free T_4, and 24-h urine free cortisol were also evaluated. Patients were considered responsive to the TRH and/or GnRH test when a GH increase of at least 50% and higher than 6 μg/l over the basal value was found, according to worldwide accepted criteria (6). In 42 patients a follow-up study was repeated 1 month after octreotide withdrawal.

Magnetic resonance or CT of the hypothalamic–pituitary region with contrast media were done at baseline and after 12 months of treatment. Tumor

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Effects of treatment with octreotide in acromegalic patients—a multicenter Italian study

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Treatment of acromegaly is effective in reversing the reduced life-span of patients only when serum growth hormone (GH) concentrations are lowered to less than 2.5 μg/l. Usual treatments achieve this goal in no more than 50–60% of patients. The effects of octreotide were studied in a prospective, open label study with 68 acromegalic patients enrolled in 10 Italian centers. Octreotide was administered sc at a dose of 100 μg t.i.d. for 1 year. After 3 months of therapy, octreotide was effective in decreasing serum GH levels below 2.5 μg/l in 16 out of 64 acromegalic patients (25%). Fifteen of them had pretreatment GH levels below 25 μg/l. Insulin-like growth factor I (IGF-I) levels normalized in about 40% of patients. No further GH reduction was observed after 1 year of treatment. The presence of abnormal GH responses to thyrotropin-releasing hormone (TRH) and gonadotropin-releasing hormone was reduced from 54 to 24% and from 16 to 12%, respectively. Tumor shrinkage was observed in 50% of 26 non-irradiated patients after 12 months of treatment. Both basal and TRH-stimulated serum prolactin levels significantly decreased in the 11 hyperprolactinemic patients. Although serum thyrotropin, free triiodothyronine and free thyroxine concentrations were not modified, a significant reduction of thyrotropin response to TRH was observed in the 9th month of therapy. In non-diabetic patients, an increase of mean blood glucose levels without modifications of fasting morning concentrations was found. About one-quarter of the patients with overt diabetes mellitus had an impairment of their metabolic control. Main clinical symptoms of acromegaly improved in 70–80% of patients. An 18% decrease of low-density-lipoprotein cholesterol and unchanged high-density-lipoprotein cholesterol levels were observed in 35 patients studied. Triglyceride levels decreased in patients with hypertriglyceridemia pretreatment. Regarding side effects, gallstones were newly diagnosed in five patients, three patients dropped out because of severe diarrhea and two diabetic patients dropped out due to worsening of their metabolic control. In conclusion, octreotide is an effective treatment of acromegaly, mainly in patients with moderate elevation of serum GH levels. The drug has also been proved to positively affect dyslipidemia.

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Acromegalic patients have a reduced lifespan and increased morbidity compared with a normal age- and sex-matched control population (1, 2). Treatment is able to reverse this long-term poor outlook only in those patients whose serum GH concentrations are reduced to less than 2.5 μg/l (2). Usual treatments, such as neurosurgical removal of the adenoma and/or pituitary irradiation, are able to achieve this goal in no more than 50–60% of patients (3–5). According to the main clinical trials, medical treatment with dopamine agonists decreases serum GH levels below 5 μg/l in about 20% of patients but below 2.5 μg/l only in a minority of cases (6). The somatostatin analog octreotide seems to provide a more effective alternative. In fact, several studies, including some multicenter worldwide trials, have shown serum GH normalization in 16–40% of acromegalic patients (7–13). However, the effects of somatostatin analogs are not limited to GH release but also involve several other endocrine and

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volume was calculated by measuring the three major diameters (a,b,c) and applying the formula $4/3\ \pi abc/2$. Tumor shrinkage was defined as at least 10% volume reduction. Visual field examination was performed at baseline and after 12 months of treatment using either Goldman's perimetry or computer-assisted static perimetry, depending on the local practice in each study center.

Owing to the high prevalence of goiter in acromegaly, a thyroid ultrasonography was done in 54 patients at baseline. The examination was repeated after 12 months of therapy in 32 patients.

Weight, pulse rate, blood pressure, signs and symptoms of the disease were evaluated at baseline and every 3 months during treatment. To assess drug efficacy on clinical manifestations of acromegaly, the main signs and symptoms, including hypertension, headache, fatigue, paresthesias, musculoskeletal pain, hyperhidrosis, modifications of the menstrual cycle in women and loss of libido and/or potency in men, were scored according to the following scale: 0, absent; 1, improved; 2, unchanged; 3, worsened. In addition, the circumference of the middle phalanx of the fourth finger of the left hand was measured.

Adverse events were evaluated by assessing symptoms and by measuring main hematological and biochemical parameters at baseline and at each control. Gallbladder ultrasonography was done at baseline and repeated at 6 and 12 months of therapy. Asymptomatic gallstones were not considered a contraindication to the administration of octreotide; however, two patients were submitted to therapy with bile acids along with the somatostatin analog.

Hormone assays

Hormone measurements were carried out by RIA and IRMA methods at each study center (see Appendix). The standards utilized by six of the ten centers were calibrated against the WHO 1st IRP IIGH-MRC 66/217. However, four centers used standards calibrated against NIH IRP 80/505. The equivalence between the two standards is clearly stated by the manufacturers (1 ng of 80/505 = 0.85 ng of 66/217). The laboratories participated in a common quality control system that gave a CV below 20% for all the concentrations tested (1.5, 20 and 40 μg/l). Owing to the different methodologies for IGF-I assay (some requiring extraction and some not), implying differences in the normal range, no absolute values were given for IGF-I concentrations. In each patient the age-adjusted normal range for each individual laboratory was referred to.

Statistical analyses

Statistical analyses of pretreatment and end-of-study results were performed only for patients for whom complete information was available. Descriptive continuous variables (weight, height, blood pressure, heart rate and BMI) and efficacy variables (mean levels of IGF-I, free T_3 and free T_4) were analyzed by factorial analysis of variance. Data with multiple observations for each time (GH, glucose, insulin, TSH, TRH-stimulated fT_3 and fT_4, PRL) were quantified by measuring the area under the curves (AUC) using the trapezoidal method. Areas and the mean GH and PRL levels were compared using non-parametric statistics within treatment: Wilcoxon's signed rank test (two means comparison) or Freedman's test (more than two means). Symptoms and signs of acromegaly were evaluated by McNemar's test of symmetry between pretreatment and the end of the study. The contingency tables (2×2) related to GH levels vs tumor shrinkage were evaluated by Fisher's exact test.

All results are expressed as mean $\pm$ SD, unless otherwise stated.

Results

Effects on GH and IGF-I levels after 3 months of therapy

Sixty-five patients completed the first 3 months of the study, 64 taking a dose of 300 μg/day. Serum GH levels (mean of nine samples taken hourly during saline infusion) decreased from 32.5 ± 54 to 13.2 ± 26 μg/l, with a percentage mean decrease of 57 + 29%. Serum GH concentrations were reduced by over 50% in 43 patients (67% of total). Mean serum GH levels below 2.5 μg/l were observed in 16 patients (25%), of whom 15 had pretreatment serum GH levels below 25 μg/l. When excluding previously irradiated cases, 63% of patients decreased serum GH levels by more than 50%, while a reduction to less than 2.5 μg/l was achieved in 24% of patients. One patient that received a dose of 50 μg twice a day because of gastrointestinal side effects had only a temporary effect on GH secretion after each injection.

No correlation between the GH percentage decrease and pretreatment GH levels was found. However, in the 16 patients who had a fall in serum GH levels to 2.5 μg/l or less, pretreatment GH levels were significantly lower than those found in the 17 patients with serum GH levels still higher than 5 μg/l (12 ± 10 vs 61 ± 91 μg/l; $p < 0.05$).

No statistical differences in GH responsiveness to somatostatin were found between patients submitted to previous treatments or not. In fact, the mean percentage decrease of serum GH levels was $56 \pm 23\%$ in irradiated vs $55 \pm 28\%$ in non-irradiated patients; in operated patients it was $55.9 \pm 24\%$ vs $53.8 \pm 30\%$ in non-operated patients; in subjects previously treated with dopaminergic drugs it was $54.5 \pm 24\%$ vs $55.3 \pm 30\%$ in those untreated. However, patients previously

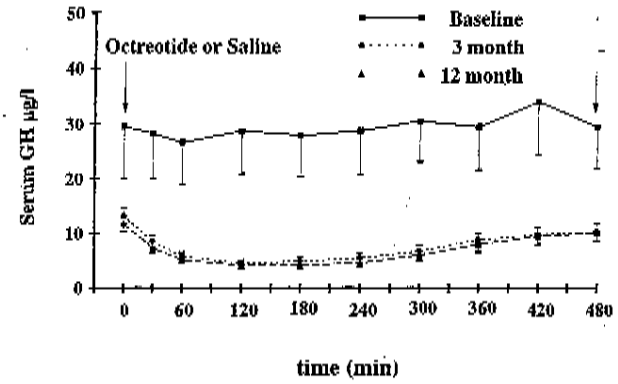

Fig. 1 Mean serum GH levels (± SEM) during an 8-h saline control before treatment and during chronic octreotide therapy in 50 acromegalic patients who completed 12 months of treatment. Serum GH concentrations at 3 months of therapy were superimposable to those found at 12 months.

submitted to other forms of therapy reached absolute GH concentrations lower than untreated patients.

After 3 months of therapy the IGF-I levels normalized in about 40% of patients (21/53), a percentage that does not change when considering only non-irradiated patients (19/48). The IGF-I levels normalized in all the patients with mean GH concentrations $\leq 2.5\,\mu g/l$ and in 10 out of 18 patients with serum GH levels between 2.6 and $7.0\,\mu g/l$. A positive correlation between IGF-I and GH percentage decrease was found ($r = 0.38$, $p < 0.01$).

Effects on GH and IGF-I levels after 12 months of therapy and during the follow-up

Fifty patients completed the study and received octreotide therapy for 12 months. In these patients, mean GH levels were not significantly different from those observed at 3 months (7.0 ± 5.9 vs $7.7 + 6.2\,\mu g/l$, respectively) (Fig. 1), with a percentage mean decrease of $58 \pm 33\%$. Mean GH concentrations lower than $2.5\,\mu g/l$ were found in 20% of patients. However, in some patients a further decrease in serum GH levels was seen between the 3rd and the 12th month; in particular, two patients who were unresponsive at the 3rd month showed a 50% decrease in serum GH levels at the 12th month. On the contrary, one patient became completely refractory.

As far as modifications of octreotide doses are concerned, a loss of efficacy was observed in two of the four patients who had a reduced daily dose of octreotide. In none of the nine cases in whom the daily dose was increased (up to $600\,\mu g$/day) were serum GH levels normalized ($9.9 + 3.3$ vs $8.6 \pm 3.5\,\mu g/l$; NS). Another two patients discontinued the drug: one for inefficacy and one due to non-compliance.

One month after therapy withdrawal, mean serum GH levels returned to baseline in the majority of patients while 40% of irradiated patients and 25% of untreated patients maintained reduced GH concentrations (50–85% of pretreatment levels); 14% of untreated patients showed GH concentrations 60–120% higher than baseline.

The mean IGF-I levels measured in 42 patients after 12 months of therapy were not significantly different from those found after 3 months. However, six patients normalized the IGF-I level between the 3rd and the 12th month of therapy, out of a total of 24 (57%) patients with normal IGF-I levels (three dropped out during the same period).

Abnormal GH responses to TRH, GnRH and OGTT

Before starting octreotide treatment, 35/65 patients (54%) increased serum GH levels from 22.6 ± 32 to $83.2 \pm 11\,\mu g/l$ after TRH administration and 10/63 (16%) from 15.2 ± 7 to $40.8 \pm 22\,\mu g/l$ after GnRH administration. After 9 months of therapy the abnormal GH responses to TRH and GnRH were reduced from 54% to 24% and from 16% to 12%, respectively. The TRH test became negative in 17 out of 28 retested patients, showing an abnormal GH increase before therapy (Fig. 2). Mean serum GH levels were slightly, although not significantly, lowered in 17 patients in whom the abnormal response disappeared, in comparison to 11 patients in whom the response was maintained ($5.1 + 6$ vs $8.8 + 6.9\,\mu g/l$; $p = 0.06$). The GnRH test became negative in two our of eight retested patients, although mean GH levels were still elevated. Responsiveness to octreotide evaluated as percentage mean GH decrease after 3 months of therapy, was $58 \pm 27\%$ and $67 \pm 18\%$ in patients who at baseline had shown a paradoxical GH increase after TRH and GnRH, respectively, and $51 \pm 27\%$ and $52 \pm 26\%$, respectively, in patients who did not. These differences were not statistically significant.

In 18 out of 35 patients (51%) GH levels decreased to less than $2\,\mu g/l$ after a glucose load. Fourteen of these patients had reached mean GH levels below $5\,\mu g/l$ during the 3-month evaluation.

Effects on tumor mass

Twenty-six patients with pituitary imaging positive for tumor (17 macroadenomas and nine microadenomas) had a comparative CT or MR study at 12 months. None had received previous pituitary radiotherapy. Thirteen (50%) of these patients showed a reduction of tumor mass: in four cases the image of a microadenoma completely disappeared; in three cases (two macroadenomas and one microadenomas) the tumor shrinkage was greater than 50% and in the remaining patients (three macroadenomas and three microadenomas) the tumor size was reduced by 10–15%. In two cases with a decrease lower than 20% a radiological examination performed 1 month after the withdrawal of octreotide therapy

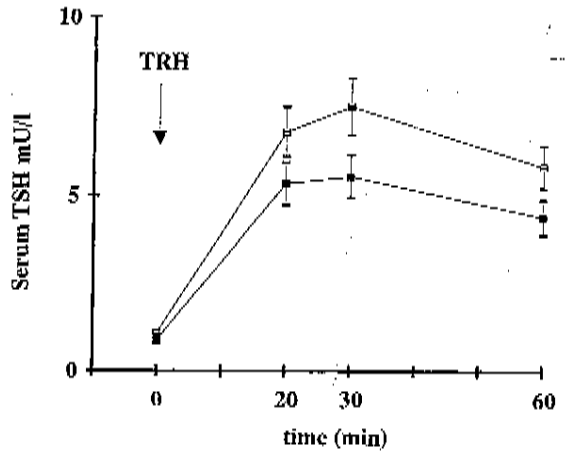

Fig. 4. Thyrotropin response (+ SEM) to TRH before (□) and after 9 months of octreotide therapy (■) in 32 acromegalic patients. A significant reduction was seen during chronic therapy.

TRH-stimulated TSH secretion was seen at 9 months (Fig. 4).

No significant modifications of basal levels of fI_3 and fT_4, evaluated every 3 months during therapy in 30 patients, were seen. Free T_4 and fI_3 responses to TRH was evaluated only in 14 patients: a small, though not significant, decrease of fT_4 response was found (47.5± 14.2 vs 42.8 ± 11.3 pmol l^{-1} h^{-1}).

Thyroid ultrasonography at baseline showed the presence of goiter in 76% of patients: simple in 46% of patients and multinodular in 30% of patients. When reinvestigated after 12 months of therapy, six patients (18%) showed a reduction in goiter size while eight patients (25%) showed an increase in goiter size and/or the appearance of new nodules. No correlation between the modifications of thyroid size or morphology and IGF-I/GH levels was found.

Effects on insulin and glucose metabolism in non-diabetic patients

Twenty acromegalic patients without overt diabetes mellitus had hourly determinations of glucose and insulin levels at baseline, 3 and 12 months. While no modifications of fasting morning glucose concentrations were seen (4.88 ± 0.5, 4.72 ± 0.6 and 4.77± 0.6 mmol/l respectively, at baseline, 3 and 12 months), a slight increase of both pre-prandial and post-prandial mean glucose levels reaching statistical significance at 3, but not at 12 months, was observed during octreotide therapy (8-h AUC: 44.4 ± 5, 47 ± 4 and 45.4 ± 5 mmol/l l^{-1} h^{-1}, respectively). The increase in blood glucose concentrations was accompanied by a significant reduction in insulin levels (8-h AUC: 1643 ± 1226 vs 1018 ± 502 vs 975 ± 466 pmol l^{-1} h^{-1}, respectively; baseline vs 3 months, $p < 0.05$; baseline vs 12 months, $p < 0.01$; 3 vs 12 months, NS).

As far as the response to the OGTT is concerned, during treatment both the blood glucose peak at 2 h and the AUC were increased in comparison with the baseline test (glucose peak: 9.8 ± 2.8 vs 6.9 ± 2.2 mmol/l, $p < 0.01$; AUC: 32.4 ± 6 vs 26 ± 5.8 mmol l^{-1} h^{-1}, $p < 0.01$). Individual data showed a worsening of the response in about one-third of patients (according to the National Diabetes Data Group criteria, eight previously normal patients fulfilled the criteria of impaired glucose tolerance, and seven patients the diabetes mellitus classes), while a normalization of the response was seen in three patients. In none of the patients was reactive hypoglycemia seen. Insulin release after glucose load was significantly reduced during octreotide therapy with respect to baseline (1076 ± 767 vs 1765± 1348 pmol l^{-1} h^{-1}; $p < 0.01$). No significant changes of glycosylated hemoglobin were observed during octreotide therapy in the 34 patients having the evaluation performed (5.2 ± 0.9 at baseline vs 5.1 + 1.1% at 12 months).

Effects on insulin and glucose metabolism in diabetic patients

Fifteen acromegalic patients had non-insulin-dependent diabetes mellitus, while one had insulin-dependent diabetes mellitus before starting octreotide therapy. In four of these patients a clear worsening of metabolic control was observed: one required a threefold increase in his daily insulin dose, one had to be treated with insulin therapy at high doses and two patients had octreotide withdrawn because of worsening of serum glucose levels. In contrast, in two patients an improvement was seen because glycosylated hemoglobin normalized without changing daily doses of oral antidiabetic drugs and diet. Three dropped out for unrelated reasons and in the remaining seven patients no significant modifications of carbohydrate control and drug requirement were seen.

Effects on lipid metabolism

Mean serum total and LDL cholesterol levels significantly decreased after 3 months of octreotide treatment: from 5.35 ± 1 to 4.88 ± 1 mmol/l ($p < 0.05$) and from 3.33 ± 1 to 2.71 ± 0.9 mmol/l ($p < 0.05$), respectively, in 35 patients studied. No further significant modifications of both parameters were seen between 3 and 12 months of therapy. Mean HDL cholesterol levels were unaffected by octreotide treatment (pretreatment: 1.29 ± 0.4 mmol/l; 3 months: 1.34 ± 0.3 mmol/l; 12 months: 1.34 ± 0.3 mmol/l). Individual data show that 22/35 patients had basal serum total cholesterol levels >5.2 mmol/l, which were normalized by treatment in 14 patients, remained unchanged in six and slightly increased in two patients. As far as triglyceride levels are concerned, a slight but not significant decrease was

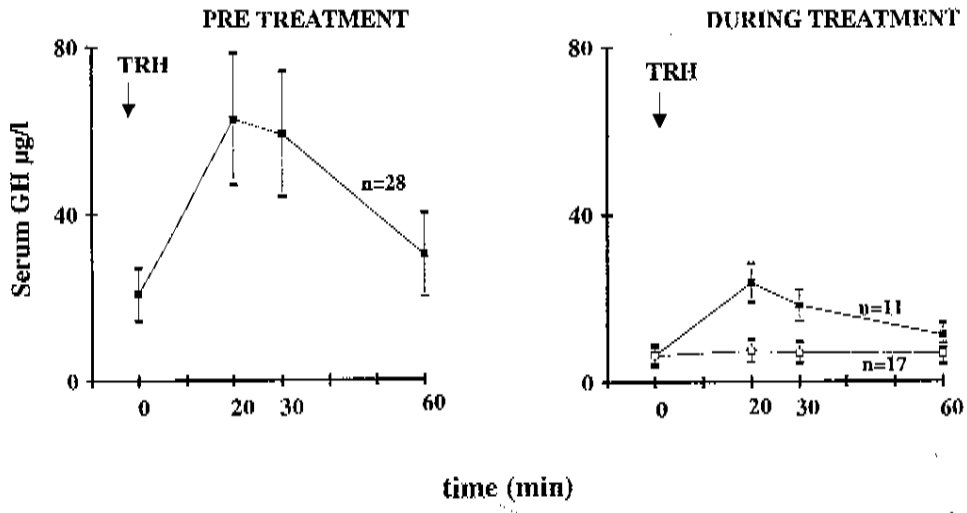

Fig. 2. Growth hormone response (± SEM) to TRH before (on the left) and during chronic octreotide therapy in 28 retested patients showing an abnormal GH increase before treatment. The abnormal response disappeared in 17 patients (□) and was maintained in 11 (■)

documented the re-expansion of the tumor mass up to the original size. All the four patients in whom the tumor image disappeared had normalized serum GH levels. In the other patients no correlation between tumor mass reduction and GH decrease was observed. On the whole, tumor disappearance or shrinkage was observed in 11/19 (58%) patients who reduced serum GH levels by 50% or more, and 2/7 (28.5%) patient who did not. Considering the absolute serum GH levels, tumor disappearance or shrinkage was observed in 5/8 (62.5%) patients who reduced GH levels to below 2.5 µg/l and 8/18 (44%) patients who maintained GH levels higher than 2.5. No statistical difference between groups was achieved.

Effects on PRL secretion

Serum PRL levels were affected differently by octreotide treatment, depending on patients being hyper- or normoprolactinemic at baseline. Serum PRL levels decreased in 11 hyperprolactinemic patients from 53.6 ± 45 (range 20–184) to 26.7 ± 26 µg/l (range 8–103) at 3 months ($p < 0.01$) and normalized in five patients. The TRH test was repeated after 9 months of octreotide therapy in nine cases and showed a significant reduction in PRL response (AUC = 39.1 ± 27.9 vs 70.3 ± 49.2 $\mu g l^{-1} h^{-1}$; $p < 0.01$). On the contrary, no significant modification of either basal or TRH-stimulated serum PRL levels was seen in 34 normoprolactinemic patients (AUC after TRH: 17.9 ± 10.5 vs 19.1 ± 10.6 $\mu g l^{-1} h^{-1}$) (Fig. 3).

Effects on thyroid function and ultrasonography

No significant changes of TSH secretion were found during chronic treatment with octreotide in 32 euthyroid patients not taking thyroid hormone therapy (8-h AUC: 6.4 ± 3.3 at baseline; 5.8 ± 3.4 at 3 months and 6.5 ± 4.1 $\mu U ml^{-1} h^{-1}$ at 12 months). A significant reduction of

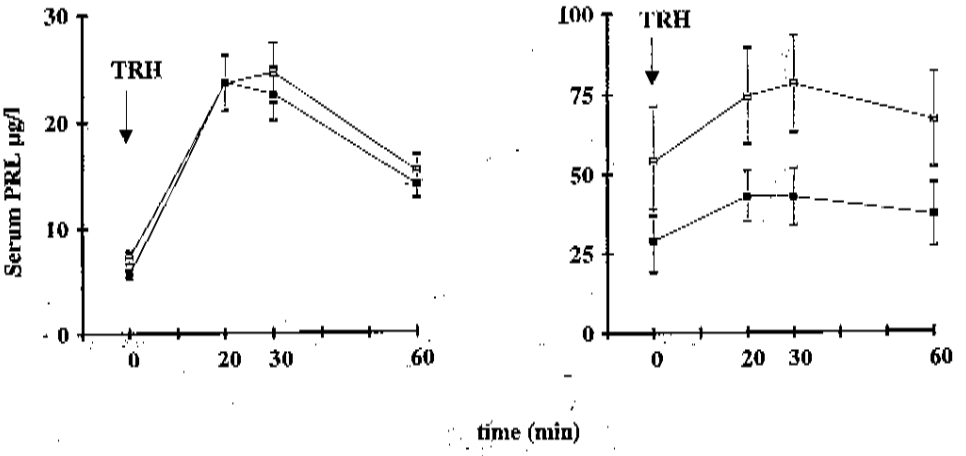

Fig. 3. Prolactin response (± SEM) to TRH before (□) and during (■) octreotide therapy in 34 normoprolactinemic (*left*) and in nine hyperprolactinemic (*right*) acromegalic patients. A significant reduction of PRL response was seen only in hyperprolactinemic patients.

seen in the whole group (pretreatment: 1.63 ± 0.9 mmol/l; 3 months: 1.55 ± 1 mmol/l; 12 months: 1.37 ± 0.5 mmol/l), while a significant reduction (2.13 ± 0.3 vs 1.38 ± 0.5 vs 1.44 ± 0.3 mmol/l; $p < 0.01$) was seen in 10 patients who had pretreatment plasma triglycerides levels > 1.8 mmol/l. Normal triglyceride levels were reached in nine of these patients.

Other clinical effects

Body mass index significantly decreased during octreotide therapy from 26.6 ± 3.7 to 25.7 ± 3.2 at 12 months ($p < 0.01$). A slight, but not significant, decrease of both systolic and diastolic blood pressure was seen (from 131 ± 16 to 127 ± 13 mmHg and from 83 ± 9 to 80 ± 9 mmHg, respectively). An improvement or the disappearance of the main symptoms of acromegaly was reported by the majority of patients: about 80% for hyperhidrosis, paresthesias and headache and about 70% for fatigue and musculoskeletal pain. Clinical symptoms improved not only in all patients in whom mean GH levels decreased by 50% or more, but also in some patients with a very slight and short-lasting octreotide effect on GH secretion. Hypertension improved in 5/14 patients (two with GH levels below 2.5 μg/l, two with GH levels between 2.5 and 5 μg/l and one with unmodified GH concentrations) and worsened in one case in spite of a 65% GH decrease. Alterations of the menstrual cycle, loss of libido and loss of potency were not influenced by the treatment. The circumference of the middle phalanx of the left hand fourth finger decreased in about 80% of patients, while it was unchanged in 15% and it increased in 5% of patients who maintained elevated GH levels during octreotide therapy. During octreotide therapy, visual field defects disappeared in 4/11 patients (36%) who decreased their mean GH levels by 48–98% without however reaching mean GH levels below 2.5 μg/l, while bitemporal hemianopsia was observed in two out of the 27 patients (7%) who had a normal visual field at baseline despite GH levels being decreased by 62–86%.

Side effects and drop-outs

Diarrhea and abdominal pain were reported by 53% and 26% of the patients at the beginning of treatment. These symptoms required permanent or temporary withdrawal of octreotide therapy in seven cases. However, in the other patients they spontaneously remitted after 7–14 days. At 12 months, diarrhea and abdominal pain occurred in only 6% and 8% of patients, respectively. Nausea was reported by about 8% of patients during all the study and pain at the site of injection by 4–10% of the patients. Five patients (10%) showed the appearance of gallstones during octreotide therapy: two at the ultrasonography performed at 6 months and three at the 12-month examination. No ultrasonographic changes were observed in the four patients who had gallstones before starting therapy.

During the first 3 months of therapy, three patients discontinued the treatment because of severe diarrhea, complicated in one case by enteritis. At 12 months, 14 patients had dropped out: two diabetic patients due to worsening of their metabolic control; two patients because neoplastic diseases were discovered (one lymphoma and one colon cancer); three because they were non compliant with treatment; four wanted to undergo pituitary adenomectomy, although two of them had a very good response to octreotide therapy; two because of inefficacy; one patient died due to unrelated causes (bronchopneumonia).

Discussion

The efficacy of octreotide in the treatment of acromegalic patients has been clearly demonstrated since the first studies were performed (8, 10, 11). The criteria used in order to define the normalization of serum GH levels are still controversial and not unequivocal in different studies. The recent demonstration that mean concentrations of GH below 2.5 μg/l, but not higher levels, are associated with a life expectancy similar to that calculated for a control population (2) prompted us to choose this threshold value in defining the efficacy of the drug. Unlike other multicenter studies, we also decided to analyze separately the data of non-irradiated patients in order to avoid the bias resulting from GH decline that is known to persist over years after radiotherapy. In our study, a chronic treatment with octreotide administered sc for 3 months at the dose of 300 μg/day reduced the average GH levels to less than 2.5 μg/l in 24% of non-irradiated patients, so only one-quarter of acromegalic patients indeed reached "safe" GH levels. These data accord with those of previous large case studies, although the criteria chosen are not coincident. In fact, Ezzat et al. (9) and Sassolas et al. (12) found GH normalization, defined as mean serum GH levels of 2 μg/l or less, in 16–26% of patients, depending on the doses used and the time of treatment. In our study, mean serum GH levels were reduced by over 50% in 63% of patients not previously irradiated. This figure is somewhat lower than those (71% and 74%, respectively) reported by Ezzat et al. (9) and Vance et al. (13) in two large case studies that included several previously irradiated patients. Our figure is more similar to the 56% found by Sassolas et al. (12). We did not find any correlation between the degree of responsiveness to octreotide, evaluated as serum GH percentage decrease, and pretreatment serum GH levels. However, safe GH levels were almost exclusively obtained in patients with pretreatment values lower than 25 μg/l. As a consequence, previously treated patients starting from lower serum GH levels more easily reached safe GH concentrations in comparison with untreated patients.

It has been hypothesized that the magnitude of GH reduction during octreotide therapy is dependent on time (10, 13). This is not confirmed by our data. In fact, apart from a few exceptions, mean GH concentrations after 12 months of treatment were fully comparable to those found after 3 months. However, because previous studies were carried out for 18–24 months, it cannot be excluded that a longer course of therapy is necessary before obtaining a further reduction of GH levels. In one case an escape from octreotide suppression was observed at 12 months.

On the whole, IGF-I levels were normalized in 40% of patients. It is worth mentioning that several patients normalized their IGF-I levels in spite of the persistence of pathological serum GH levels. This is in agreement with previous studies (8, 9, 13, 16, 17) and supports the hypothesis of a direct effect of octreotide on IGF-I production and IGF-I binding proteins (18, 19). A crucial issue is the relative importance of GH levels below 2.5 μg/l with respect to normalized IGF-I levels for clinical and lifespan benefits in acromegalic patients. This point could be clarified only by specific studies.

Our finding of a reduction of tumor size in 50% of 26 non-irradiated patients with identifiable tumor is in agreement with previous reports (7–14). In our experience, microadenomas had a greater probability to be reduced than macroadenomas, which is at variance with previous observations (12). The degree of reduction of the tumor volume did not correlate with the magnitude of GH suppression, as already observed by others (9). In addition, no statistical difference between patients with or without GH reduction by 50% or more and with and without GH reduction to below 2.5 μg/l was achieved, thus suggesting that the control of GH secretion does not offer better chances for a tumor to shrink.

No significant modifications of either basal or TRH-stimulated PRL levels was seen in 34 normoprolactinemic patients, confirming that octreotide does not act on normal lactotroph cells. On the contrary, a significant octreotide-induced reduction of basal PRL levels was seen in hyperprolactinemic patients, as already described (12, 20, 21). It is widely recognized, as also confirmed by our own data, that elevated PRL levels in acromegalic patients maintain responsiveness to TRH stimulus (22, 23), at variance with the high PRL levels of patients with pure PRL-secreting adenomas in whom a lack of effect of octreotide was also described (20). Following octreotide administration we observed a significant reduction of PRL response to TRH in the hyperprolactinemic patients. These findings suggest that octreotide is able to suppress PRL release from mixed GH- and PRL-secreting adenomas. This is in agreement with previous observations in patients in whom the presence of mammosomatotrophs cells has been documented by in vitro studies of the tumor (20).

As far as the effects of octreotide on TSH secretion and thyroid function are concerned, our study confirms that basal serum TSH, fT_3 and fT_4 release are not modified by chronic octreotide therapy, in agreement with previous studies (9, 21, 24–26). A reduction in circulating total T_3 levels, suggesting a decreased peripheral conversion of T_4 to T_3, has been described (24, 26). These variations are probably very transitory (26), while our first measurements of thyroid hormone levels were performed after 3 months of treatment. We found a significant reduction of TRH-stimulated TSH secretion after 9 months of treatment. Blunting of TSH response to TRH has been described previously after short-term octreotide administration (25). However, these subtle octreotide-induced alterations of the hypophyseal–thyroid axis do not seem to provoke abnormalities in thyroid function.

Goiter is far more frequent in acromegalic patients than in normal subjects. In our series goiter was found in 76% of patients, a percentage higher than reported previously (27). This may result from either the high prevalence of endemic goiter in Italy or the use of thyroid ultrasonography for diagnosis. The results of 12-month octreotide therapy on the goiter size and/or the number or size of thyroid nodules show a great individual variability but, on the whole, no significant changes were observed. These results seems to disprove the role of IGF-I in the pathogenesis of goiter (28).

Octreotide treatment was very effective in improving other symptoms typical of acromegaly. Even if serum GH levels were halved in only 60% of patients, hyperhidrosis, headache, fatigue and paresthesias improved in about 80% of patients, perhaps better reflecting the effect on tissue IGF-I levels. Hypertension improved in 10% of patients. Only a few previous studies report on serum lipid changes in acromegalic patients treated with octreotide. A slight, but not significant, reduction in serum cholesterol levels has already been described (29). In our series the reduction of total and LDL cholesterol was significant and a decrease in serum triglycerides was observed in hypertriglyceridemic patients, in agreement with other reports (12, 29). Owing to the increased prevalence of cardiovascular diseases in acromegaly, the observed lipid changes are of particular importance and deserve further investigation. In fact, although the explanation of the observed changes could be partly ascribed to a reduction of fat absorption (12, 30), it probably also involves other still unknown effects of octreotide.

In accordance with other studies we have at first observed a high incidence of gastrointestinal complaints, particularly diarrhea, but this tended to subside. An initial lower dosage of octreotide, gradually increasing to the full dose, or alternatively, a temporary reduction of the dosage might be useful in order to overcome the problem. In our series, 9% of patients showed evidence of asymptomatic cholelithiasis before entering the study. The observation is comparable to what is seen in non-acromegalic individuals in the Italian population (31). However, the presence of

patients with prolactinomas and acromegaly. Clin Endocrinol (Oxf) 1986;25:201–12
21. Page MD, Millward ME, Taylor A, Preece M, Hourihan M, Hall R, et al. Long-term treatment of acromegaly with a long-acting analogue of somatostatin, octreotide. Q J Med 1990;74:189–201
22. Lamberts SWJ, Klijn JGM, Kwa GH, Birkenhäger JC. The dynamics of growth hormone and prolactin secretion in acromegalic patients with "mixed" pituitary tumours. Acta Endocrinol (Copenh) 1979;90:198–210
23. Bassetti M, Arosio M, Spada A, Brina M, Bazzoni N, Faglia G, et al. Growth hormone and prolactin secretion in acromegaly: correlations between hormonal dynamics and immunocytochemical findings. J Clin Endocrinol Metab 1988;67:1195–201
24. Roelfsema F, Frölich M. Pulsatile thyrotropin release and thyroid function in acromegalics before and during subcutaneous octreotide infusion. J Clin Endocrinol Metab 1991;72:77–82
25. Christensen SE, Weeke J, Kaal A, Harris AG, Ørskov H. SMS 201-995 and thyroid function in acromegaly: acute, intermediate and long-term effects. Horm Metab Res 1992;24:237–9
26. Christensen SE, Weeke J, Ørskov H, Kaal A, Lund E, Jørgensen J, et al. Long-term efficacy and tolerability of octreotide treatment in acromegaly. Metabolism 1992;41 Suppl 2:44–50
27. Nabarro JDN. Acromegaly. Clin Endocrinol (Oxf) 1987;26:481–512
28. Bidey SP. Control of thyroid cell and follicle growth. Recent advances and current controversies. Trends Endocrinol Metab 1990;1:174–8
29. Cohen R, Chanson P, Bruckert E, Timsit J, Legrand A, Harris AG, et al. Effects of octreotide on lipid metabolism in acromegaly. Horm Metab Res 1992;24:397–400
30. McGregor AR, Troughton WD, Donald RA, Espiner EA. Effect of the somatostatin analog SMS 201-995 on faecal fat excretion in acromegaly. Horm Metab Res 1989;22:55–6
31. The MICOL Group. Prevalence of gallstone disease in 18 Italian population samples: first results from the MICOL study. In: Capocaccia L, et al. editors. Recent advances in the epidemiology and prevention of gallstone disease. The Netherlands: Kluwer Academic, 1991:37–44
32. Dowling RH, Hussaini SH, Murphy GM, Besser GM, Wass JAH. Gallstones during octreotide therapy. Metabolism 1992;41 Suppl 2:22–33
33. Ho KK, Jenkins AB, Furler SM, Borkman M, Chrisholm DJ. Impact of octreotide, a long-acting somatostatin analogue, on glucose tolerance and insulin sensitivity in acromegaly. Clin Endocrinol (Oxf) 1992;36:271–9
34. Koop BL, Harris AG, Ezzat S. Effect of octreotide on glucose tolerance in acromegaly. Eur J Endocrinol 1994;130:581–6
35. Heron I, Thomas F, Dero M, Gancel A, Ruiz JM, Schatz B, et al. Pharmacokinetics and efficacy of a long-acting formulation of the new somatostatin analog BIM 23014 in patients with acromegaly. J Clin Endocrinol Metab 1993;76:721–7
36. Morange I, De Boisvilliers F, Chanson P, Lucas B, Dewailly D, Catus F, et al. Slow release lanreotide treatment in acromegalic patients previously normalized by octreotide. J Clin Endocrinol Metab 1994;79:145–51

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asymptomatic gallstones does not seem to represent a contraindication to octreotide therapy, because no impairment of ultrasonography or appearance of specific symptoms was seen during the course of the study. Conversely, gallstones were newly diagnosed in five cases (10%), an incidence similar to that reported in other studies (7, 9, 12, 14, 32). Suppression of the meal-stimulated release of cholecystokinin, gallbladder hypomobility, development of supersaturated bile and possible other mechanisms might all be involved in the pathogenesis of cholelithiasis during octreotide treatment (32).

The influence of octreotide on carbohydrate metabolism appears more complex. On the whole we observed, at variance with others (33, 34), and increase of mean blood glucose levels during octreotide therapy in non-diabetic patients. In patients with overt diabetes mellitus we found an impairment of metabolic control in about 25%, with two patients discontinuing the treatment, while beneficial effects on carbohydrate metabolism in acromegalic patients with glucose intolerance are usually described (33, 34).

In conclusion, we confirm that octreotide is an effective tool in the medical treatment of acromegaly, improving the clinical symptoms in the majority of patients and normalizing GH levels in about one-quarter and IGF-I levels in about 40% of cases. Lower pretreatment serum GH concentrations seem to be associated with the most beneficial effects. The drug has also been proved to positively affect dyslipidemia, a major risk factor for cardiovascular disease that represents the most frequent cause of death in acromegalic patients. One of the major limitations of octreotide therapy appears to be the timing of administration: the requirement for frequent daily injections. Preliminary data show that this limitation could be overcome in the future by the use of depot formulations (35, 36).

Appendix

The following kits were used:

(i) For GH assay: "IIGH Allegro" IRMA Nichols Institute (USA); "Seria HGH" IRMA Ares Serono (Italy); "HGH" RIA Ares Serono (Italy); "HGH lisophase" RIA Technogenetics (Italy); HGH-CTK IRMA Sorin Biomedica (Italy).

(ii) For IGF-I assay: "Somatomedin C" RIA Nichols (USA); 'Somatomedina C MAB" IRMA Medical System (Italy); "Somatomedin C" RIA Incstar (USA).

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References

1 Alexander L, Appleton D, Hall R, Ross WM, Wilkinson R. Epidemiology of acromegaly in the Newcastle region. Clin Endocrinol 1980;12:71–9

2 Bates AS, Van'T Hoff W, Jones JM, Clayton RN. An audit of outcome of treatment in acromegaly. Q J Med 1993;86:293–9

3 Davis DH, Laws Jr ER, Ilstrup DM, Speed JK, Caruso M, Shaw EG, et al. Results of surgical treatment for growth hormone-secreting pituitary adenomas. J Neurosurg 1993;79:70–5

4 Fahlbusch R, Honegger J, Buchfelder M. Surgical management of acromegaly. Endocrinol Metab Clin North Am 1992;21:669–92

5 Eastman RC, Gorden P, Glatstein E, Roth J. Radiation therapy of acromegaly. Endocrinol Metab Clin North Am 1992;21:693–712

6 Faglia G, Arosio M, Ambrosi B. Recent advances in diagnosis and treatment of acromegaly. In: Imura H, editor. Pituitary gland. 2nd ed. New York: Raven Press, 1994:411–51

7 Barkan AL, Kelch RP, Hopwood NJ, Beitins IZ. Treatment of acromegaly with the long-acting somatostatin analog SMS 201-995. J Clin Endocrinol Metab 1988;66:16–23

8 Chiodini PG, Cozzi R, Dallabonzana D, Oppizzi G, Verde G, Petroncini M, et al. Medical treatment of acromegaly with SMS 201-995, a somatostatin analog: a comparison with bromocriptine. J Clin Endocrinol Metab 1987;64:447–53

9 Ezzat S, Snyder PJ, Young WF, Boyajy LD, Newman C, Klibanski A, et al. Octreotide treatment of acromegaly. A randomized, multicenter study. Ann Intern Med 1992;117:711–8

10 Lamberts SWJ, Uitterlinden P, del Pozo E. SMS 201-995 induces a continuous decline in circulating growth hormone and somatomedin-C levels during therapy of acromegalic patients for over two years. J Clin Endocrinol Metab 1987; 65:703–10

11 Plewe G, Beyer J, Krause U, Neufeld M, del Pozo E. Long-acting and selective suppression of growth hormone secretion by somatostatin analogue SMS 201-995 in acromegaly. Lancet 1984;2:782–4

12 Sassolas G, Harris AG, James-Deidier A. Long term effect of incremental doses of the somatostatin analog SMS 201-995 in 58 acromegalic patients. J Clin Endocrinol Metab 1990; 71:391–7

13 Vance ML, Harris AG. Long-term treatment of 189 acromegalic patients with the somatostatin analog octreotide. Results of the international multicenter acromegaly study group. Arch Intern Med 1991;151:1573–8

14 Lamberts SWJ. The role of somatostatin in the regulation of anterior pituitary hormone secretion and the use of its analogs in the treatment of human pituitary tumors. Endocr Rev 1988;9: 417–36

15 Gyr KE, Meier R. Pharmacodynamic effects of Sandostatin in the gastrointestinal tract. Metabolism 1992;41 Suppl 2:17–21

16 Lamberts SWJ, Uitterlinden P, Verleun T. Relationship between growth hormone and somatomedin-C levels in untreated acromegaly, after surgery and radiotherapy and during medical therapy with Sandostatin (SMS 201-995). Eur J Clin Invest 1987;17:354–9

17 Quabbe H-J, Plöckinger U. Dose-response study and long term effect of the somatostatin analog octreotide in patients with therapy-resistant acromegaly. J Clin Endocrinol Metab 1989;68: 873–81

18 Flyvbjerg A, Jorgensen KD, Marshall SM, Ørskov H. Inhibitory effect of octreotide on growth hormone-induced IGF-I generation and ovarian growth in the hypophysectomized rats. Am J Physiol 1991;260:F568–74

19 Ezzat S, Ren SG, Braunstein GD, Melmed S. Octreotide stimulates insulin-like growth factor-binding protein-1: a potential pituitary-independent mechanism for drug action. J Clin Endocrinol Metab 1992;75:1459–63

20 Lamberts SWJ, Zweens M, Klijn JGM, Van Vroonhoven CCJ, Stefanko SZ, Del Pozo E. The sensitivity of growth hormone and prolactin secretion to the somatostatin analogue SMS 201-995 in