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Acromegaly : treatment and follow-up : the Leiden studies

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Intravenous octreotide test predicts the long term outcome of treatment with octreotide-long-acting repeatable in active acromegaly

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ABSTRACT

OBJECTIVE: Depot formulations of somatostatin analogues are increasingly used in the treatment of active acromegaly. A priori knowledge of the efficacy of these drugs in controlling GH excess is clinically relevant, because only ~60% of the patients respond with adequate control of GH (GH levels <5 mU/L) and/or IGF-1 levels upon this treatment. Therefore, we assessed the acute responses of serum GH levels to a new octreotide test (intravenous administration of 50 µg) in 98 consecutive patients with active acromegaly and we measured the predictive value of this test for the efficacy of chronic octreotide-long acting repeatable (octreotide-LAR) treatment in 18 patients.

DESIGN: Serum GH concentrations were measured before and at 20, 30, 45, 60, 90, 120, 150 and 180 min following 50 µg i.v. octreotide. The minimal achieved GH was used for analysis. Octreotide-LAR was individually titrated aiming at a normal serum IGF-I for age and a serum GH <5 mU/L. The mean of 3–6 monthly serum GH and IGF-I measurements after individual dose adjustment was used for evaluating the efficacy of chronic therapy.

RESULTS: Octreotide decreased GH levels to values below 5 mU/L in only 49% of unselected consecutive patients and the response was inversely related to basal GH levels. In patients with baseline GH above 50 mU/L, 50 µg i.v. octreotide reduced GH to <5 mU/L in only 15% of cases (n = 41), whereas in patients with baseline GH levels below 50 mU/L this goal was achieved in 77% of cases. The fractional decrease in GH levels upon octreotide injection was similar in microadenomas and macroadenomas.

The minimally achieved serum GH concentration during the intravenous octreotide test was a good predictor for the GH concentrations during long-term octreotide-LAR treatment as assessed in 18 patients. The intravenous octreotide test, using a minimal GH level of <5 mU/L, had a sensitivity, positive and negative predictive value of 100% for prediction of GH suppression to below 5 mU/L during long term octreotide-LAR treatment. For predicting the response of IGF-I during long-term treatment, the test performed with a sensitivity of 73% and a positive predictive value of 73%.

CONCLUSION: Intravenous octreotide reduces GH to concentrations <5 mU/L in ~50% of consecutive patients with active acromegaly, which predicts a good response to chronic octreotide-LAR treatment.

Keywords: GH; Acromegaly; Octreotide; Treatment

INTRODUCTION

Acromegaly is a disorder caused by GH hypersecretion from a pituitary adenoma. Treatment with somatostatin analogues is increasingly considered as an initial treatment of acromegaly (1 – 4). Most medically treated acromegalic patients are currently prescribed a long-acting repeatable somatostatin analogue. Because it takes several months before steady state plasma concentrations of somatostatin analogues are reached, the effects of treatment on GH and IGF-1 levels can only be evaluated after 3–4 months. However, only ~60% of the patients with acromegaly have a good response to long-acting somatostatin analogues as defined by GH concentrations below 5 mU/L and/or normal, age-adjusted IGF-I concentrations (5, 6). Therefore, it is clinically relevant to predict the efficacy of chronic treatment with long-acting somatostatin analogues from the results of a simple test.

Few studies have compared the GH response to subcutaneously administered octreotide with long-term sc octreotide treatment (7, 8). However, there are no data on dynamic tests with octreotide predicting the efficacy of long-acting depot formulations of octreotide. The subcutaneously injected octreotide may have confounded the interpretation of responsiveness of the adenoma due to a less than 100% biological availability and, consequently, a longer duration of the test may be required following sc injection. Therefore, we studied the characteristics of an i.v. octreotide test on plasma GH levels, using an intravenous bolus injection of 50 µg octreotide to assure immediate and total biological availability of the drug. The first aim of the study was to establish the spectrum of responses to the new i.v. octreotide test in a large consecutive cohort of active acromegalic patients, not pre-selected for octreotide sensitivity. The second aim was to assess the predictive value of this i.v. octreotide test for the efficacy of long-term treatment with octreotide-long-acting repeatable (octreotide-LAR).

PATIENTS AND METHODS

Patients and treatment protocol

The i.v. octreotide test was performed in 98 consecutive patients with active acromegaly, who were evaluated in the Leiden University Medical Centre. Eighty-seven patients were referred prior to any treatment for GH excess and 11 patients had been treated previously for acromegaly, but had persistent (n = 7) or recurrent disease (n = 4). The i.v. octreotide test was part of the baseline biochemical and dynamical characterisation of their GH secreting adenoma, which also included an oral glucose tolerance test (GTT) and measurements of IGF-I, IGFBP-3, prolactin and other pituitary hormones. There were 53 male patients and 45 female patients and the mean age at the time of assessments was 46 ± 1.4 years (range 19–77 years).

After the octreotide test, the initial treatment was transsphenoidal microsurgery performed by a single neurosurgeon in 90% of patients (up to 1998). In case of persistent or recurrent

acromegaly, patients were treated mostly by somatostatin analogues. From 1998 onwards, patients underwent either surgery or were primarily treated by somatostatin analogue depot preparations. Monthly im depot injections of octreotide, Octreotide-LAR (Sandostatin LAR®, Novartis Pharma, Basle, Switzerland), were available from 1998 onwards and before 1998 patients were treated by subcutaneous octreotide.

Informed consent was obtained from all patients.

Octreotide-LAR treatment

In order to compare the response to the acute i.v. octreotide test with chronic octreotide-LAR treatment, all consecutive acromegalic patients who started octreotide-LAR treatment in the period 1998–2001 and had an i.v. octreotide test were selected. Two patients with radiotherapy two years before octreotide-LAR and 8 patients with surgical intervention between octreotide test and treatment were excluded. Eighteen patients were included. These patients were treated by octreotide-LAR for a mean duration of 4.1 ± 0.4 years. The choice to start with octreotide LAR treatment was not dependent on the result of the i.v. octreotide test in any of the cases. Octreotide-LAR treatment was commenced for persistent (n = 3), or recurrent (n = 4) disease, or as primary medical treatment preferred over surgery by physician and/or patient (n = 11). Octreotide-LAR treatment was started at a dose of 20 mg per month and was individually adjusted aiming at random serum GH concentrations below 5 mU/L and a normal IGF-I for age. Four of the 18 patients had an episode of subcutaneous octreotide treatment of 2 (3 patients) and 4 years (1 patient) prior to the start of octreotide-LAR treatment.

Tests

Baseline evaluation

Octreotide test: Serum GH levels were measured just prior to and 15, 30, 45, 60 min after i.v. injection of 50 µg of octreotide, and thereafter every 30 min for 2 additional hours (duration of test: 3 h). For this study, we used the basal serum GH and the nadir GH measured during the test to calculate the fractional (%) and absolute decrease in GH concentration.

Evaluation of octreotide-LAR treatment

Biochemical and clinical evaluation was performed at 3-month intervals in the titration phase and thereafter twice a year. Most patients were studied at day 28, just before a new injection. All measurements were performed in a steady state condition after at least 3 monthly injections during a four weekly injection scheme. Random GH and IGF-I concentrations were measured with 3–6 months intervals during therapy with octreotide-LAR. Most patients had five treatment evaluations during octreotide treatment. The mean number of evaluations was 4.3 ± 1.3 (range: 2–5) for GH and 4.1 ± 1.5 (range: 1–5) for IGF-I. The range of follow-up

during LAR treatment was 4 months to 5.7 years (median 4.6 years). The fractional decrease from pre-treatment GH/IGF-I concentrations to octreotide-LAR suppressed GH/IGF-I concentrations were used for analysis and compared to the GH response during the i.v. octreotide test. The mean of all serum GH and IGF-I concentrations measured at consecutive visits during octreotide-LAR treatment after dose titration was established was used for analysis.

Assays

All GH concentrations were measured with a sensitive, time-resolved fluoroimmunoassay, specific for the 22 kDa GH protein (Wallac, Turku, Finland). This assay uses recombinant human (rh)GH as standard, which is calibrated against World Health Organisation First International Reference Preparation (No. 80–505). The detection limit was 0.03 mU/L (for conversion from mU/L to µg/L divide by 2.6). The inter-assay coefficients of variation (CVs) were 1.6–8.4% in the concentration range of 0.25 and 40 mU/L. According to current opinion in the literature, we considered serum GH level <5 mU/L (equivalent to 1.9 µg/L) as adequate suppression during medical therapy (9 – 11).

The total serum IGF-I concentration was determined by RIA after extraction and purification on ODS-silica columns (Incstar Corp., Stillwater, MN). 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 from 137 healthy controls aged 20–80 years (12).

Prolactin concentrations were measured with a sensitive time-resolved fluoroimmunoassay (Wallac, Turku, Finland). The standards were calibrated against the World Health Organization third International Standard for Prolactin (No. 84/500). The interassay CV varied from 2.0% to 3.3% in the assay range from 3.0 to 80 µg/L. The limit of detection was 0.04 µg/L. Normal levels are below 6 µg/L in males and below 11 µg/L in females.

Statistical analysis

Data are expressed as means ± SEM, unless otherwise stated. The responses of serum GH during different stimulation tests were expressed as absolute decreases and fractional decreases. Data were analysed with ANOVA, linear and logistic regression techniques. $P < 0.05$ was considered to represent statistical significance.

RESULTS

Baseline characteristics

Mean age of patients was 46.0 ± 1.4 years in 98 patients (53 males, 45 females). Their mean serum GH concentration was 80.3 ± 10.8 mU/L at baseline, and the mean prolactin concentration 23.5 ± 10.7 µg/L. Twenty-seven patients had a microadenoma, 51 a macroadenoma and 20 an invasive macroadenoma.

Intravenous Octreotide test in unselected patients with active acromegaly (Fig. 1)

The acute i.v. octreotide test was well-tolerated and no adverse events occurred during the tests. Intravenous octreotide decreased GH concentrations to values below 5 mU/L in 49% of consecutive patients and to values below 2 mU/L in 28% of patients (Fig. 1). The efficacy of intravenous octreotide to decrease GH to values below 5 mU/L was inversely related to basal GH levels ($R = -0.98$, $P < 0.001$). In patients with a basal GH > 50 mU/L, a serum GH < 5 mU/L was achieved in only 15%, while in patients with a GH < 50 mU/L this was achieved in 77%.

In the patients who responded with GH levels < 5 mU/L after octreotide administration, a serum GH < 5 mU/L was achieved at 30 min in 48% of the patients, at 60 min in 73%, at 90 min in 86% of the patients, and finally only at 120 min in a subset of 14% of patients. As shown in Fig. 2, mean minimal values were achieved after 60–90 min and these were maintained for the duration of the test. The maximal suppressive effect of octreotide (nadir GH) was achieved only after 2 h in 56% of patients, i.e., at 2 h in 18.5%, at 2.5 h in 21% and at 3 h in 16% of patients.

Baseline GH concentrations and the absolute decrease in serum GH concentrations were significantly higher in macroadenomas than in microadenoma in previously untreated patients ($P = 0.003$ and $P = 0.003$, respectively), but the fractional decrease was not different between micro- and macro-adenomas. The basal GH concentration was the only significant and independent factor predicting normalisation of GH concentration, defined as a minimal serum GH below 5 mU/L, during the acute i.v. octreotide test (odds ratio 1.011 (95% confidence interval: 1.003–1.018), $P = 0.004$). Logistic regression analysis did not identify age,

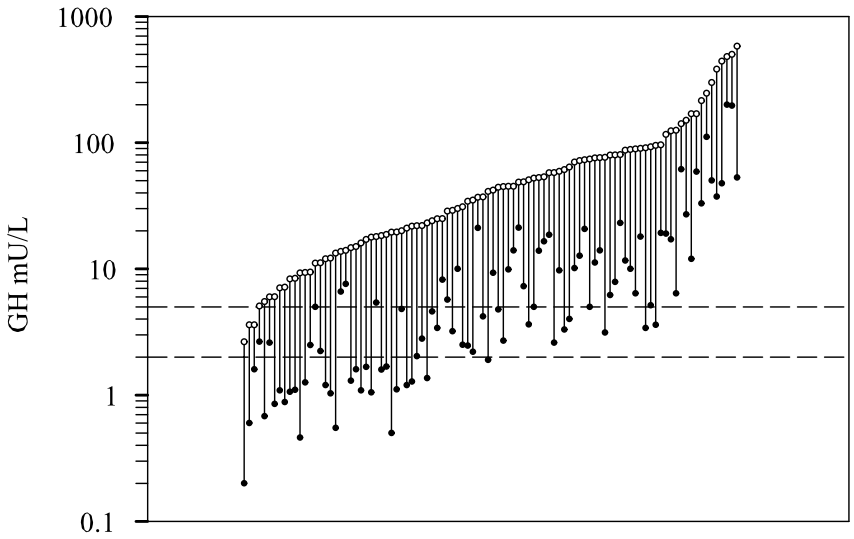

Figure 1. Maximal decrease of GH concentrations in 98 acromegalic patients after i.v. injection of 50 µg octreotide. The basal GH concentration is shown as open circles and nadir concentration by the closed circles. Fifty-two patients were able to suppress their GH below 5 mU/L (upper horizontal line) and 27 patients below < 2 mU/L (lower horizontal line).

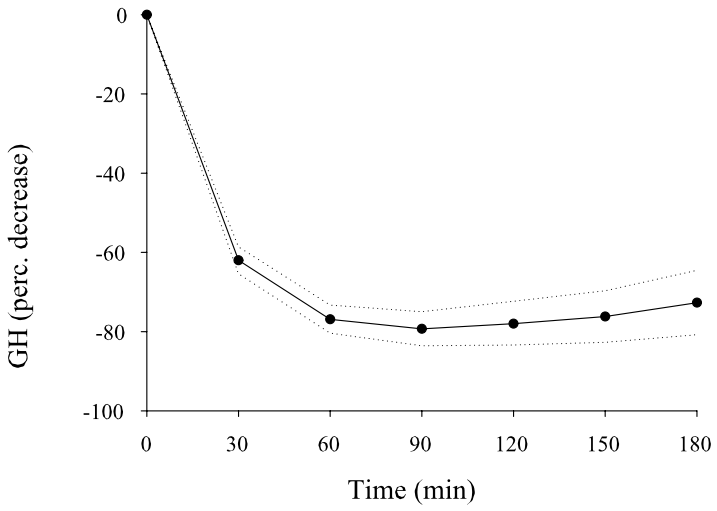

Figure 2. Mean relative decrease in GH concentration during the octreotide test. X-axis: time points of GH measurements (0, 30, 60, 90,120, 150, 180 minutes). Y-axis: relative decrease from baseline (0%) expressed as mean (solid line) and lower and upper 95% confidence intervals (dotted lines).

sex, tumour class or prolactin concentration as independent factors for the response to i.v. octreotide. The nadir serum GH concentration during the octreotide test was not correlated to the serum IGF-I concentration.

The predictive value of the octreotide test for the response to octreotide-LAR treatment in 18 patients

Chronic treatment with octreotide-LAR injections resulted in a serum GH below 5 mU/L in 11 out of 18 patients (61%). A normal serum IGF-I for age was observed in an equal number of patients (61%), although discrepant findings in normalisation of serum GH and IGF-I were present in 6 patients (33%). No significant differences for age, tumour class, sex, basal serum GH or IGF-I concentration were observed between patients responding to octreotide treatment with a serum GH <5 mU/L and those who did not. No side effects occurred during the long-term octreotide-LAR treatment in this study, except for self-limiting mild bowel complaints in the beginning of treatment.

The GH response to intravenous octreotide was compared with chronic octreotide-LAR treatment at an individually adjusted optimal dose in 18 patients (10 mg n = 1, 20 mg n = 12, 30 mg n = 5). In these 18 patients, GH concentrations decreased by 86% (from 51 ± 23 to 6.4 ± 2.7 mU/L) during the acute octreotide test and a comparable decrease was observed during chronic octreotide-LAR treatment (80 ± 3.6%). The mean decrease in serum IGF-I concentration was 39 ± 6.3% during chronic octreotide-LAR treatment. The fractional decrease in GH concentrations during the acute i.v. test was strongly correlated with the fractional decrease in GH concentrations during octreotide-LAR treatment ($R = 0.75$, $P < 0.001$, Fig. 3). There was no relationship between baseline GH and serum GH concentrations during octreo-

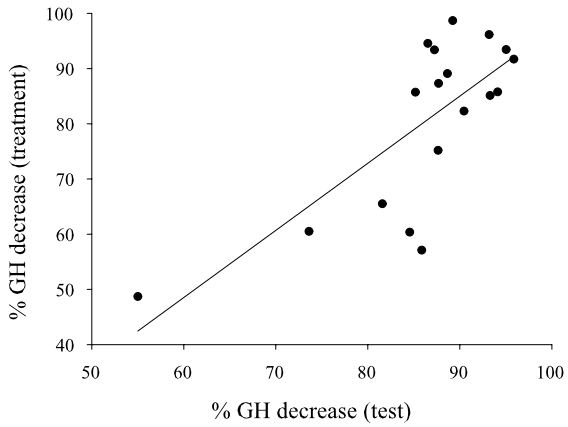

Figure 3. Scatter plot of the relative decrease during the i.v. octreotide test and during chronic octreotide treatment with octreotide-LAR in 18 patients. A significant correlation was present for the response to the acute iv test and chronic octreotide-LAR treatment (R= 0.75, P<0.001)

tide treatment, while there was a significant positive correlation between basal serum IGF and serum IGF-I concentration during treatment (R = 0.506, P = 0.032). However, the predictive value of both the basal serum IGF-I and GH concentration before start of treatment for the response to octreotide-LAR treatment were very poor.

All 11 patients with a suppressed GH below 5 mU/L in the acute test, achieved a normal serum GH level (<5 mU/L) on chronic octreotide-LAR treatment (n = 11). On the other hand, all 7 patients with a minimal GH level equal or above 5 mU/L during the test, had serum GH concentrations above 5 mU/L during chronic treatment (Fig. 4), corresponding with a sensitivity and specificity of 100%. A more stringent test threshold of <2.5 mU/L was also associated with a sensitivity and specificity of 100% for achieving a serum GH < 2.5 mU/L during chronic LAR treatment (n = 18). Characteristics of the octreotide test (threshold GH < 5 mU/L) for the prediction of a normal IGF-I during treatment were: sensitivity 73%, specificity 57%, positive predictive value (PPV) 73% and negative predictive value (NPV) 57%. For a serum GH threshold of below 2.5 mU/L the test characteristics for predicting a normal IGF-I were: sensitivity 73%, specificity 71%, with a PPV 80% and a NPV 63%. A more stringent criterion was thus not associated with improved predictive value.

DISCUSSION

The i.v. octreotide test decreased baseline GH levels to below 5 mU/L in almost half of the patients in an unselected cohort of consecutive patients with active acromegaly. In addition, the i.v. octreotide test excellently predicted the suppression of GH concentrations by long-term treatment with octreotide-LAR, although limited predictive value was present for the IGF-I concentration during chronic treatment.

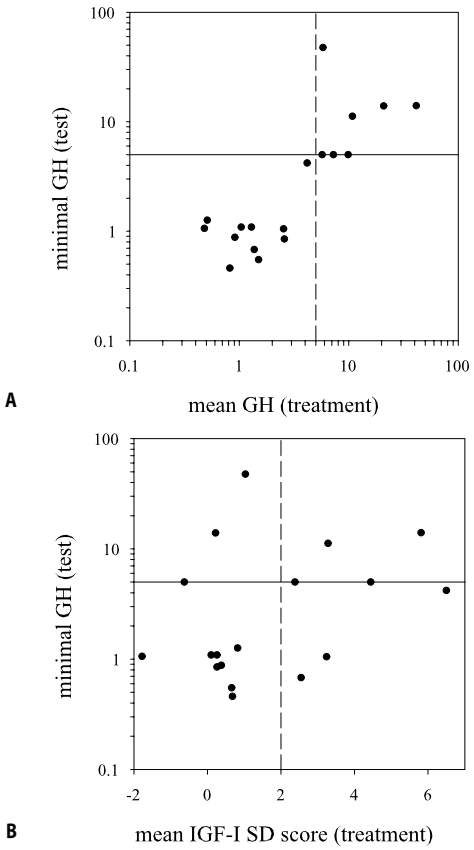

Figure 4. Relationship between the minimal GH concentration (in mU/L) during the octreotide test and mean GH concentration (in mU/L) during therapy with octreotide-LAR (a) and corresponding mean IGF-I SD score (b).

After the first description of somatostatin receptors in pituitary tumours of acromegalic patients and the linear relationship between receptor density and GH inhibition, now almost 20 years ago, the discovery of the various subtypes of the somatostatin receptor was extremely important for understanding the clinical efficacy of somatostatin and its analogues (13 – 15). In addition, the development of new, differentially selective drugs has opened new therapeutic perspectives (16). In GH-secreting pituitary adenomas there is a good correlation between the in vivo response to subcutaneously administered octreotide and the mRNA expression of SSTR2 and SSTR5 (18). Heterogeneity of receptor subtype expression contributes to the varying GH suppression of somatostatin analogues in vivo and in vitro between patients (17 – 19).

In response to i.v. octreotide, even though GH secretion was inhibited by at least 40% in all unselected acromegalic patients, we also observed variation in GH suppression. Other series found generally lower numbers of octreotide responsive patients, varying from 56% to 67%

(defined by a GH decrease of 50% or more) (8, 20, 21). Generally, these patient series were smaller, and either native somatostatin-14 was infused intravenously, or octreotide was given subcutaneously, which may explain the observed discrepancies. A suppression to <5 mU/L after i.v. octreotide occurred within 60 min in 73% of patients and within 2 h in all patients achieving this arbitrary cut-off level. Therefore, when octreotide is given by an i.v. bolus, a 2-h test suffices for the determination of octreotide sensitivity, at least when the cut-off point of <5 mU/L is used. Interestingly, about half of patients had an ongoing suppressive effect with maximal GH suppression after 2 h or more following the i.v. octreotide bolus.

Most studies assessing efficacy of octreotide-LAR treatment studied patients preselected on the basis of octreotide sensitivity, which was tested in most cases by the acute GH response to a subcutaneous injection (5). Since the i.v. octreotide test well reflects the response to chronic therapy, an interesting outcome of this study in unselected consecutive patients is the high percentage of responders, especially in those with lower baseline serum GH concentrations.

A GH concentration below 5 mU/L during chronic therapy is frequently proposed to delineate normalisation of the increased mortality risk in surgically treated patients (9 – 11). However, recent studies suggest more stringent criteria (22, 23). The best biochemical aim for medical treatment remains to be established and may be more stringent than a serum GH < 5 mU/L. Nevertheless, a serum GH < 5 mU/L was used in most studies on efficacy of octreotide-LAR and therefore we focus on this criterion in the present report. This arbitrary value of a GH < 5 mU/L was achieved in ≈50% of the patients during the i.v. octreotide test, but unfortunately this goal is infrequently reached when basal GH levels exceed 50 mU/L. A more stringent criterion, a minimal GH concentration of <2 mU/L, was achieved in only 28% of the patients, mostly in those patients with a basal GH concentration less than 25 mU/L. These figures correspond with the reported response rates in chronic sc octreotide and octreotide-LAR studies which use a mean serum GH < 5 mU/L and a normal IGF-I concentration as criteria for control (1, 6, 24, 25). These observations also underline the advantage of debulking the adenoma by surgery in many patients with high GH concentrations, even when they are octreotide-sensitive. The predictive findings of the octreotide test and the used cut-off points are probably also applicable in patients with post-operatively residual active disease, as can be expected from pre- and post-operative data in a few patients (data not shown).

The predictive value of the acute i.v. octreotide test for achievement of a normal IGF-I during treatment was less favourable than for achievement of a serum GH < 5 mU/L. Discrepant findings regarding the normalisation of serum IGF-I and achievement of a serum GH < 5 mU/L have been reported previously (25 – 30). The relation between serum GH and IGF-I concentrations is not straightforward. The discrepancies may be explained first by the fact that a serum GH of 5 mU/L or less may not reflect a normalised GH production. Other important factors that may influence the relation between serum GH concentration and GH dependent IGF-I production are age, sex and differences in gonadal status (31 – 34). In general, we advise to

increase the octreotide-LAR dose and if necessary to add Pegvisomant when IGF-I remains elevated but serum GH is below 5 mU/L.

The minimally achieved, absolute serum GH concentration during the intravenous octreotide test corresponds well with the effect of long-term treatment with octreotide-LAR. A reliable predictive test for the efficacy of octreotide-LAR and comparable drugs, including slow release formulations of lanreotide, is clinically important, as evaluation of treatment is only possible after a steady state is reached after at least 3–4 months of treatment. This intravenous octreotide-sensitivity test can be useful to identify patients eligible for primary medical treatment with octreotide-LAR. Comparable results were reported by Lamberts et al. (7) who found a good predictive value of the subcutaneous octreotide test for the efficacy of long term treatment with short-acting, subcutaneous octreotide, when a decrease in serum GH of 50% was achieved. However, others could not find such a relationship (8). As lanreotide and octreotide share the same octreotide receptor subtype profile, it is likely that the results in this study are also applicable for lanreotide, although not formally investigated.

The evaluation of octreotide-LAR treatment was performed in most cases on day 28 after an injection in a steady state condition. However, in a previous study serum IGF-I, GH and octreotide concentrations did not differ between 2 and 4 weeks following an injection (35). Therefore, the time point of evaluation is probably not relevant once there is a steady state condition.

In summary, in unselected, consecutive acromegalic patients intravenous octreotide reduced GH concentrations below 5 mU/L in half of the patients, even though octreotide reduced GH concentrations by more than 50% in almost all patients. This was explained at least in part by the limited efficacy of intravenous octreotide to reduce GH levels below 5 mU/L in patients with high basal GH levels. This i.v. octreotide test is useful to predict the long-term outcome of octreotide-LAR treatment for suppression of GH concentration. A limited predictive value was present to indicate the response of serum IGF-I during long-term octreotide-LAR treatment in this small cohort. Further research in a larger cohort of octreotide-LAR treated patients is required to assess which cut-off point for the i.v. octreotide test is best to identify those patients who will achieve a normal IGF-I concentration during treatment.

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