Long-Term Remission of Acromegaly after Octreotide Withdrawal Is an Uncommon and Frequently Unsustainable Event

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Key Words

Acromegaly · Octreotide · Remission · Somatostatin analog

Abstract

Background: Long-term remission of acromegaly after somatostatin analog withdrawal has been reported in 18–42% of patients in studies with a relatively small number of patients using different inclusion and remission criteria. The objectives of this study were to establish the probability and predictive factors for short- and long-term remission [normal IGF-1 for age/sex: $\text{IGF-1} \leq 1.00 \times$ upper limit of normal (ULN)] after octreotide long-acting release (LAR) withdrawal in a larger population of well-controlled patients with acromegaly (normal mean IGF-1 in the last 24 months). **Methods:** This is a prospective multicenter study in which 58 well-controlled patients with acromegaly receiving only octreotide LAR as a primary or postsurgical treatment were included in

14 university centers in Brazil. All patients had been on stable doses and dose intervals of octreotide LAR in the last year, and none had been submitted to radiotherapy. The main outcome measure was serum IGF-1 after 8 weeks (short-term) and 60 weeks (long-term) of octreotide LAR withdrawal. **Results:** Seventeen of 58 patients (29%) were in remission in the short term, and only 4 patients achieved long-term remission after treatment withdrawal. The Kaplan-Meier estimated remission probability at 60 weeks was 7% and decreased to 5% at 72 weeks. The short-term remission rate was significantly higher (44%; $p = 0.017$) in patients with pre-treatment IGF-1 $< 2.4 \times$ ULN. No other predictive factor for short- or long-term remission was found. **Conclusion:** Our results show that long-term remission of acromegaly after

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octreotide LAR withdrawal was an uncommon and frequently unsustainable event and do not support the recommendation of a systematic withdrawal of treatment in controlled patients.

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Introduction

Somatostatin analogs (SAs) are considered the first-line medical therapy in the treatment of acromegaly [1, 2]. They can be used as an adjunct treatment after unsuccessful surgery, while awaiting the long-term effects of radiotherapy, and as a primary treatment [3–5]. The mechanisms of action of SAs in acromegaly include the inhibition of growth hormone (GH) secretion by the tumor and, to a lesser extent, inhibition of IGF-1 secretion by the liver [6, 7]. SAs have also been shown to exhibit in vitro antiproliferative, apoptotic, and antiangiogenic effects in pituitary adenomas [8]. Nonetheless, the duration of SA treatment in acromegaly has usually been thought to be lifelong in nonirradiated patients, which significantly increases the financial cost and treatment burden to patients [9, 10].

Prolactinomas were the first pituitary tumors to be successfully treated with pharmacological treatment, and dopamine agonists have been shown to induce remission after treatment withdrawal. In a recent meta-analysis, remission rates of 16 and 21% have been found for macro- and microprolactinomas, respectively [11]. More recently, in acromegaly, long-term hormonal remission has been reported in 18–42% of patients after SA treatment withdrawal [12–15]. Those studies, however, included a relatively small number of patients with diverse inclusion and remission criteria.

The aim of this study was to assess the probability of remission after octreotide long-acting release (LAR) withdrawal in a large population of well-controlled patients with acromegaly. This study is part of a prospective multicenter study of remission of acromegaly after withdrawal of different medical treatments.

Materials and Methods

Study Overview

We conducted the study from December 13, 2012, through September 30, 2015, at 14 university referral centers for pituitary diseases from 10 cities in 8 states in Brazil. The protocol was approved by each local ethics committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Fig. 1. Flow chart showing the selection process of our study population of 58 well-controlled patients with acromegaly on octreotide LAR treatment.

The 2 investigators from the coordinator site (A.C. and J.A., Universidade Federal de São Paulo) were responsible for project design, data collection, monitoring, and analysis, as well as manuscript preparation. A committee including A.C., J.A., and 6 other investigators was established to further review the manuscript before its submission to all participants for formal approval.

Patients

Figure 1 shows the selection process of our study population of 58 patients with acromegaly on octreotide LAR treatment, drawn from a larger population of 97 well-controlled patients with acromegaly after exclusion of screening failures [IGF-1 $>1.00 \times$ upper limit of normal (ULN) at screening visit], previous radiotherapy, and treatment with cabergoline either alone or in combination with octreotide LAR. All these patients had also met the initial inclusion criteria: primary or adjuvant treatment with octreotide LAR for ≥ 24 months, dose and dose interval unchanged in the last 12 months, mean IGF-1 $\leq 1.00 \times$ ULN (patient's mean IGF-1 divided by IGF-1 ULN for age and sex) in the previous 24 months, and IGF-1 $\leq 1.00 \times$ ULN at the screening visit. No patient had any of the exclusion criteria (pregnancy, current use of pegvisomant, and pituitary tumor distance to the optic chiasm <5 mm). All patients provided written informed consent before participation.

Study Protocol

Patients were assessed by clinical examination and biochemical measurements at 0, 8, 16, 24, 36, 48, 60, 72, and 84 weeks after treatment withdrawal (the first assessment at week 8 corresponds to 12 weeks after the last injection). A pituitary MRI was obtained at 48–60 weeks for patients in remission.

After treatment withdrawal, patients with IGF-1 $\leq 1.00 \times$ ULN at each visit were considered to be in remission and continued without medication for acromegaly. Patients presenting with IGF-1 $>1.00 \times$ ULN during follow-up were considered relapses. All patients relapsing with IGF-1 $>1.20 \times$ ULN were restarted on octreotide LAR at the same doses as before treatment withdrawal. Pa-

Table 1. Baseline demographic characteristics in 58 well-controlled patients with acromegaly

Age at diagnosis, years	45±11 (21–71)
Age at study entry, years	54±11 (27–77)
Females	40 (74)
Macroadenoma	54 (93)
GH levels at diagnosis, ng/ml	20.3 (1.04–178)
IGF-1 at diagnosis, ×ULN	3.0 (1.4–9.1)
Diabetes mellitus type 2	22 (41)
Hypertension	33 (61)
Previous surgery	46 (85)
Tumor remnant at study entry	27 (50)
Duration of medical therapy, months	49 (24–173)
Octreotide LAR 10 mg/month	3 (5)
Octreotide LAR 20 mg/month	34 (59)
Octreotide LAR 30 mg/month	21 (36)
4-week dose interval	51 (88)
4- to 8-week dose interval	5 (8.6)
>8-week dose interval	2 (3.4)
Mean IGF-1 during 24 months before study, ×ULN	0.8±0.15 (0.28–1.00)
GH levels at study entry, ng/ml	1.14±1.2 (0.08–5.00)
IGF-1 at study entry, ×ULN	0.73±0.22 (0.16–1.00)

Continuous data are shown as means ± SD, with the exception of skewed variables (duration of medical therapy, IGF-1 and GH at diagnosis), which are shown as medians and ranges. Categorical data are presented as absolute numbers and proportions.

tients relapsing with IGF-1 levels between 1.00 and 1.20 × ULN were kept off medication unless they presented clinical signs and/or symptoms of disease activity or tumor growth.

Women on oral contraceptives or replacement therapy with oral estrogen maintained the same doses and routes of administration during the entire study. All other medications were kept or changed according to clinical judgment.

Study End Points

The prespecified primary end points of the study were the proportions of patients with serum IGF-1 within the age- and sex-adjusted normal range at 8 weeks (short-term remission) and at ≥60 weeks after drug withdrawal (long-term remission).

Secondary end points included: (1) the proportion of patients with IGF-1 within the age- and sex-adjusted normal range at each visit after therapy withdrawal; (2) clinical activity of disease as judged by the attending physician; (3) biochemical assessments [serum GH, fasting blood glucose, and glycosylated hemoglobin (HbA1c) by routinely available methods], and (4) a health-related quality of life assessment using the Acromegaly Quality of Life Questionnaire (AcroQoL), in which higher scores indicate better quality of life. All those parameters were evaluated at each visit.

In the short-term analysis, GH levels, AcroQoL, and several other parameters were compared in patients relapsing with IGF-1 levels between 1.00 × ULN and 1.20 × ULN, patients relapsing with IGF-1 >1.20 × ULN, and patients in remission. In addition, we

analyzed clinical behavior and IGF-1 levels over the entire follow-up in the subgroup of patients relapsing at any time point with IGF-1 ≤1.20 × ULN.

IGF-1 and GH Assays

Serum IGF-1 and GH were determined locally in each center using automated two-site, solid-phase, enzyme-labeled chemiluminescent immunometric assays (Immulite 2000, Siemens Healthcare Diagnostics, and Liaison auto-analyzer, DiaSorin).

IGF-1 results were expressed based on the upper limit of the reference range for age and sex and were calculated by dividing the individual IGF-1 concentration by the upper limit of the reference range for age and sex as provided by the manufacturer's information.

Statistical Analyses

The Kaplan-Meier method was used to analyze the end point remission (IGF-1 ≤1.00 × ULN). All patients who had at least one visit after the screening visit were included in the analysis. Missing values were inputted with the use of the last observation carried forward method for measurements made after the screening visit.

Comparisons between three or more groups of data were analyzed by one-way ANOVA followed by a contrast test, as indicated. Comparisons between two groups of data were analyzed by paired or unpaired t tests, as appropriate. Associations between categorical variables were assessed by Fisher's exact test. The significance level was set at $p < 0.05$ (two tailed). Data were analyzed using GraphPad Prism 5.0.

Results

The baseline characteristics of the 58 patients included in the study are shown in table 1. During follow-up, 1 patient withdrew consent for personal reasons at 8 weeks, and another patient was lost to follow-up after week 16. Both patients had normal IGF-1 levels upon their last visit. Data obtained after the predefined 60-week long-term remission time point were also analyzed.

Short-Term Remission

At week 8, which corresponds to 12 weeks after the last injection of octreotide LAR, 17 of 58 patients were still controlled (IGF-1 ≤1.00 × ULN) and considered in short-term remission. The Kaplan-Meier estimate of the probability of remission at 8 weeks was 29% (fig. 2). The IGF-1 level before octreotide LAR treatment was found to be predictive for short-term remission: all patients in short-term remission had pretreatment IGF-1 <2.40 × ULN, and having a pretreatment IGF-1 <2.40 × ULN significantly increased the probability of short-term remission to 44% ($p = 0.017$, Fisher's exact test).

No other predictive factor for short-term remission was found: gender, age, GH and IGF-1 levels at diagnosis

Fig. 2. Kaplan-Meier analysis of remission rates ($\text{IGF-1} \leq 1.00 \times \text{ULN}$) after octreotide withdrawal over 72 weeks. Arrows show the probabilities of short- and long-term remission at the prespecified time points.

and at study entry, micro- or macroadenoma at diagnosis, visible or invisible tumor remnant at study entry, diabetes, hypertension, previous surgery, AcroQol score, and dose, frequency, or duration of octreotide LAR ($0.09 < p < 1.00$). Quality of life scores (AcroQol) remained unchanged after octreotide withdrawal in patients in short-term remission (71 vs. 70, respectively; $p = 0.88$, paired t test).

Long-Term Remission

The 29% probability of remission after octreotide withdrawal at week 8 declined to 10% at week 16 and reached a plateau of 7% from week 24 through week 60, which corresponded to 4 patients in remission at week 60 (fig. 2). At 72 weeks, the probability of remission further dropped to 5%, as 1 of the 4 patients evaluated at that visit had relapsed. The only patient whose follow-up reached 84 weeks also relapsed.

No common distinctive features in relation to other patients that could be regarded as predictive for long-term remission in those 4 patients were identified. The age range was 32–61 years; 3 patients were female; 1 had a microadenoma, and 3 had macroadenomas at diagnosis. All macroadenomas had been submitted to surgery. A single patient still had a visible tumor remnant at study entry. A single patient had a microadenoma at diagnosis that had not been operated on and was no longer visible at study entry. Octreotide LAR doses were 20 or 30 mg/

Fig. 3. Follow-up of IGF-1 serum levels in 18 patients with acromegaly relapsing with IGF-1 between 1.00 and $1.20 \times \text{ULN}$ after octreotide withdrawal.

month, the dose interval was >4 weeks in only 1 patient, and treatment duration ranged from 24 to 61 months. No signs or symptoms suggestive of tumor enlargement were observed in patients on long-term remission, and pituitary MR scans performed at 48–84 weeks off treatment were unchanged.

In the 4 patients in long-term remission, the mean IGF-1 values during medical therapy and after treatment withdrawal were similar (0.78 ± 0.2 vs. $0.74 \pm 0.2 \times \text{ULN}$; $p = 0.67$, paired t test); AcroQol scores did not change significantly after octreotide withdrawal ($p = 0.46$, paired t test), but mean GH levels during the follow-up were significantly increased after octreotide LAR withdrawal (1.1 ± 0.85 vs. 1.9 ± 1.1 ng/ml; $p = 0.03$, paired t test).

Relapses with IGF-1 between 1.00 and $1.20 \times \text{ULN}$

Eighteen patients initially relapsed with IGF-1 between 1.00 and $1.20 \times \text{ULN}$: 10 patients at 8 weeks and 8 patients at later time intervals [6 patients before 60 weeks (weeks 16–24) and 2 after 60 weeks, at their last visit (weeks 72 and 84)], as shown in figure 3. During the follow-up, treatment was resumed in 10 patients when IGF-1 levels increased to $>1.20 \times \text{ULN}$ and in 2 other patients because of clinical activity of disease (headache and carpal tunnel syndrome worsening). In those patients, time to treatment after octreotide withdrawal was 30 ± 22 weeks (range 16–84). In the remaining 6 patients, IGF-1 levels remained $<1.20 \times \text{ULN}$ until their last visit (36–84 weeks).

Fig. 4. GH levels at 8 weeks after octreotide withdrawal according to IGF-1 serum levels.

As shown in figure 4, analysis of GH levels at 8 weeks showed a significant tendency ($p = 0.036$, p for trend) to decline as IGF-1 levels progressively decreased from $>1.20 \times \text{ULN}$ to $1.20\text{--}1.00 \times \text{ULN}$ in relapsing patients to $<1.00 \times \text{ULN}$ in the remission group. However, when GH levels in these three groups were compared, the only significant difference was found between patients in remission and those that relapsed with $\text{IGF-1} > 1.20 \times \text{ULN}$ (1.6 ± 1.8 vs. 3.6 ± 3.2 ng/ml; $p < 0.05$, Bonferroni test).

No differences in AcroQol scores, fasting glycemia, or HbA1c levels were found between the three groups ($p = 0.19$, $p = 0.39$, and $p = 0.70$, respectively; ANOVA). All these patients were eventually treated when their IGF-1 levels increased to $>1.20 \times \text{ULN}$ during the follow-up (9 before and a single one after 60 weeks).

Discussion

This study is, so far, the largest one to prospectively address whether long-term remission of acromegaly after SA withdrawal is a realistically achievable goal. We have used a normal sex- and age-adjusted IGF-1 level as the single remission criterion, irrespective of GH levels, because IGF-1 alone has been the major biochemical parameter to influence therapeutic decisions in acromegaly [16]. Our results have shown that long-term remission of acromegaly after octreotide LAR withdrawal is an un-

common, hardly predictable, and frequently unsustainable event in patients controlled by conventional octreotide doses and dose intervals.

The 7% long-term remission rate found at 60 weeks of follow-up in our study (64 weeks after the last injection) further decreased to 5% as patients reached 72 weeks of follow-up. These figures are lower than the 18.5–20% remission rates found in three other studies [12–14] and much lower than the 42% reported in one single report [15], but these percentage rates are derived from proportions (5/27, 4/20, 3/16, and 5/12, respectively) obtained from smaller sample sizes than in our study. In addition, these figures should not be compared without carefully analyzing differences in inclusion and remission criteria between studies.

Accordingly, the study with the highest rate included only 12 patients who had all been controlled using long dose intervals (≥ 8 weeks), a selection bias that obviously tends to overestimate the remission rate. This is in marked contrast with our study, where only 2 of 58 patients (3.4%) had been on similarly long dose intervals, and also in contrast with the other three studies, where such dose intervals were used in 10–11% of patients [12, 14] or were not used at all [13]. In addition, the inclusion of patients using cabergoline in combination with SAs in one of those studies seems inappropriate to characterize remission after SA withdrawal [13].

Another important consideration are the criteria used to define remission in the various studies. Although we have used a normal IGF-1 level as the single biochemical remission criterion, we were able to follow all patients who relapsed with IGF-1 between 1.00 and $1.20 \times \text{ULN}$, since our protocol allowed those patients to remain off treatment unless clinically indicated, which occurred in only 2 patients (11%). If we had adopted the criterion of $\text{IGF-1} < 1.20 \times \text{ULN}$, as one previous study with a remission rate of 20% did [14], we would have had 10 instead of 4 patients in remission at week 60, which would result in a more comparable remission rate of 17%. Finally, a comparison of the 18.5% remission rate observed at ≥ 12 months in the study using remission criteria of normal IGF-1 in addition to basal $\text{GH} < 2.5$ ng/ml and postglucose $\text{GH} < 1.00$ ng/ml [12] with our 7% remission rate at 60 weeks may not be truly different. In effect, these figures are not statistically different ($p = 0.10$, Fisher's exact test), reflecting overlapping confidence intervals of the two rates. After a longer follow-up, however, the two figures became more similar, as our remission rate declined to 5% (from 4 patients at 60 weeks to 3 patients at 72 weeks) and the 18.5% rate fell to 7.5% (from 5 to 2 patients in re-

mission at the last evaluation) [Spada A., Verrua E., and Mantovani G., pers. commun.].

The possibility that such a low remission rate as found in our study could result from bias should also be discussed. Using IGF-1 as a single marker of disease activity/control in the present study could potentially increase recurrence (and decrease remission rates) due to the inclusion of patients with GH levels above the suggested 'cut-off' for control (1.0 ng/dl). However, when the remission rates were calculated considering only those 35 patients entering the study with both normal IGF-1 and GH <1.0 ng/dl [4], only a single patient would be in remission using the same composite criterion, and the remission rate at 60 weeks would be 2.8 instead of 7%.

In contrast to our long-term results, an analysis of remission in the short term revealed that 29% of patients had IGF-1 $\leq 1.00 \times \text{ULN}$ at 8 weeks of follow-up (corresponding to 12 weeks after the last octreotide injection), the first evaluation after octreotide withdrawal in our study. Thus, it is likely that an even higher rate could have been achieved if the first reevaluation had been performed at a shorter time interval. At any rate, since all patients had been on the same individual doses of octreotide LAR for at least 12 months before treatment withdrawal, our short-term results suggest that a high proportion of patients should tolerate longer dose intervals of octreotide LAR, which corroborates previous studies [17–22].

The small number of patients reaching long-term remission has impaired a statistically meaningful search for predictive factors in this and other studies. Nonetheless, patients achieving short-term remission have been reported to have lower GH and/or IGF-1 levels during treatment [12–14]. Although we were not able to identify a predictive factor for long-term remission in our study, patients with lower IGF-1 levels ($<2.4 \times \text{ULN}$) before the introduction of octreotide LAR treatment showed a better probability of remission in the short term. Since being in remission in the short term is a *sine qua non* condition to reach long-term remission, lower IGF-1 values before octreotide treatment could conceivably signal a better chance of long-term remission after treatment withdrawal.

Since patients with IGF-1 $<1.20 \times \text{ULN}$ after SA withdrawal have been considered in remission in some studies [14, 15], we also analyzed their clinical and hormonal behavior throughout the follow-up. In the short term, GH levels, intermediate between patients in remission (IGF-1 $\leq 1.00 \times \text{ULN}$) and patients relapsing with IGF-1 $>1.20 \times \text{ULN}$, were highly predictive of a further IGF-1 increases to $>1.20 \times \text{ULN}$ as observed in all these patients at the following visits. Accordingly, a normal sex- and age-adjust-

ed IGF-1 level is a better criterion of remission than IGF-1 $<1.20 \times \text{ULN}$.

In conclusion, our results show that long-term remission after octreotide withdrawal in acromegaly is a rare and usually unsustainable event and do not support the recommendation of systematic withdrawal of treatment in well-controlled patients using conventional octreotide LAR doses and dose intervals. On the other hand, the much higher probability of remission in the short term may well support the strategy of routinely attempting to increase the octreotide dose interval in well-controlled patients, thus reducing the treatment burden for both patients and health systems.

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Disclosure Statement

A.C. was an employee at Novartis from January 2014 to April, 2016. M.D.B. is a consultant and a member of the Steering Committees for Chiasma, Ipsen, and Novartis. M.D.B. is a speaker for Ipsen and Novartis and a principal investigator on clinical trials for Ipsen and Novartis. M.A.C. is a consultant for Novartis, Ipsen, and Cristalia. A.R.-O. Jr. is a consultant for Novartis, Pfizer, and Ipsen. L.V. is a speaker for Novartis, Ipsen, and Pfizer. C.L.B. is a consultant and a speaker for Novartis, Ipsen, and Pfizer. P.A.C.M. is a speaker for Novartis. M.R.G. receives consulting fees, speaker fees, and research grants from Novartis, Pfizer, and Ipsen. J.A. is a principal investigator on clinical trials for Novartis and a speaker and advisory board member for Novartis and Ipsen. A.B., M.C., P.C.L.E., R.S.J., E.M.J., A.B.M., J.I.M., D.M.N., V.S.N., C.G.S.L., J.R.O.L.S., A.T., and A.B.W.T. have nothing to declare.

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