Alessandra Casagrande

REMISSÃO DA ACROMEGALIA APÓS SUSPENSÃO DO TRATAMENTO FARMACOLÓGICO: ESTUDO PROSPECTIVO MULTICÊNTRICO

Tese apresentada à Universidade Federal de São Paulo- Escola Paulista de Medicina para obtenção do titulo de Doutor em Ciências.

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Orientador:
Prof. Dr. Julio Abucham

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UNIVERSIDADE FEDERAL DE SÃO PAULO

ESCOLA PAULISTA DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM ENDOCRINOLOGIA CLÍNICA

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Dedico essa tese

A todos os profissionais e amigos endocrinologistas que dedicaram seu tempo para que esse estudo fosse possível.

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SUMÁRIO

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Artigo 1

Long-term remission of acromegaly after octreotide withdrawal is an uncommon and frequently unsustainable event

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Abbreviated Title: Acromegaly remission after octreotide withdrawal

Key terms: acromegaly, octreotide, remission, somatostatin analog

ABSTRACT

Context: Long-term remission of acromegaly after somatostatin analogs withdrawal has been reported in 18-42% of patients in studies with relatively small number of patients using different inclusion and remission criteria.

Objectives: To establish the probability and predictive factors for short-and long-term remission (normal IGF-1 for age/sex: IGF-1≤1.00 xULN) after octreotide-LAR withdrawal in a larger population of well controlled patients with acromegaly (normal mean IGF-1 in the last 24 months).

Design: Prospective, multicenter.

Settings and Participants: Fifty-eight well controlled patients with acromegaly receiving only octreotide-LAR as primary or post-surgical 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 no one had been submitted to radiotherapy.

Intervention: Withdrawal of octreotide-LAR.

Main outcome measurement: Serum IGF-1 after 8 (short-term) and 60 weeks (long-term) of octreotide-LAR withdrawal.

Results: Seventeen of 58 patients (29%) were in remission in the short-term, but only four achieved long-term remission after treatment withdrawal. Kaplan-Meier estimated remission probability at 60 weeks was 7% and decreased to 5% at 72 weeks. Short-term remission rate was significantly higher (44%, P=0.017) in patients with pre-treatment IGF-1<2.4 xULN. No other predictive factor for short- or long- term remission was found.

Conclusion: Long-term remission of acromegaly after octreotide-LAR withdrawal was an uncommon and frequently unsustainable event. In contrast, the much higher probability of short-term remission suggests that increasing dose intervals should be emphasized and routinely attempted in well controlled patients.

INTRODUCTION

Somatostatin analogs (SA) are considered the first line medical therapy in the treatment of acromegaly (1,2). They can be used as 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 SA in acromegaly include the inhibition of growth hormone secretion by the tumor and, to a lesser extent, inhibition of IGF-1 secretion by the liver (6,7). Somatostatin analogs have also been shown to exhibit *in vitro* anti-proliferative, apoptotic and anti-angiogenic effects in pituitary adenomas (8). Nonetheless, duration of SA treatment in acromegaly has usually been thought to be life-long in non-irradiated 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 (11, 12). In a recent meta-analysis, remission rates of 16% and 21% have been found for macro and microprolactinomas, respectively (13). More recently, in acromegaly, long-term hormonal remission has been reported in 18-42% of patients after SA treatment withdrawal (14-17). Those studies, however, included 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-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.

SUBJECTS AND METHODS

Study Overview

We conducted the study from December 13, 2012 through September 30, 2015, at fourteen university referral centers for pituitary diseases from ten cities in eight 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. The two investigators from the coordinator site (AC and JA, Universidade Federal de São Paulo) were responsible for project design, data collection, monitoring, and analysis, and manuscript preparation. A committee including AC, JA and six other investigators was established to further review the manuscript before its submission to all participants for formal approval.

Patients

Figure 1 shows the derivation of our study population of fifty-eight patients with acromegaly on octreotide-LAR treatment, drawn from a larger population of ninety-seven well controlled patients with acromegaly after exclusion of screen failures (IGF-1>1.00 xULN at screening visit), previous radiotherapy, treatment with cabergoline, either alone or in combination with octreotide-LAR. All those 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 ≤1.00 xULN (patient´s mean IGF-1divided by IGF-1 upper limit for age and sex) in the previous 24 months, and a confirmatory IGF-1 ≤1.00 xULN 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 ≤1.00 xULN at each visit were considered in remission and continued the study without medication for acromegaly. Patients presenting IGF-1 >1.00 xULN during follow up were considered relapses. All patients relapsing with IGF-1 >1.20 xULN were restarted on octreotide-LAR at the same doses as before treatment withdrawal. Patients relapsing with IGF-1 levels between 1.00 and 1.20 xULN 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) 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 xULN and 1.20 xULN, patients relapsing with IGF-1 >1.20 xULN, and patients in remission. In addition, we analyzed clinical behavior and IGF-1 levels along the entire follow up in the subgroup of patients relapsing at any time point with IGF-1 ≤1.20 xULN.

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 xULN). 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 among 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.

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, one patient withdrew consent for personal reasons at 8 weeks, and another one 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 xULN) and considered in short-term remission. The Kaplan-Meier estimate of the probability of remission at 8 weeks was 29% (**Figure 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 xULN and having a pre-treatment IGF-1 <2.40 xULN increased significantly 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 and at study entry, micro or macro adenoma at diagnosis, visible or not visible 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 four patients in remission at week 60 (**Figure 2**). At 72 weeks, the probability of remission further dropped to 5%, as one of the four 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 four patients were identified: age range was 32-61 years; three were female; one had a microadenoma; three had macroadenomas at diagnosis; all macroadenomas had been submitted to surgery; two patients still had visible tumor remnants 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/mo, dose interval was >4 weeks in only one patient; and treatment duration ranged from 24-61 mo. No signs or symptoms suggestive of tumor enlargement were observed in patients on long-term remission and pituitary MR scans were unchanged in the two patients who were submitted to a new MRI at 48 weeks.

In those four patients in long-term remission, mean IGF-1 values during medical therapy and after treatment withdrawal were similar (0.78±0.2 *vs* 0.74±0.2 xULN, 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 along 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 xULN

Eighteen patients initially relapsed with IGF-1 between 1.00 and 1.20 xULN: ten patients at 8 weeks and eight at later time intervals [six before 60 weeks (weeks 16-24), and two after 60 weeks, in 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 xULN and in two other patients because of clinical activity of disease. In those patients, time to treatment after octreotide withdrawal (mean ± SD) was 30 ± 22 weeks (range: 16-84 weeks). In the remaining six patients, IGF-1 levels remained <1.20 xULN until their last visit (36-84 weeks).

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 xULN to 1.20-1.00 xULN in relapsing patients to <1.00 xULN in the remission group. However, when GH levels among those three groups were compared, the only significant difference was found between patients in remission and

those that relapsed with IGF-1 >1.20 xULN (1.6±1.8 ng/ml *vs* 3.6±3.2 ng/ml, P<0.05, Bonferroni´s test).

No differences in AcroQol scores, fasting glycaemia or HbA1c levels were found among those three groups (P=0.19, P=0.39, P=0.70, respectively, ANOVA). All those patients were eventually treated when their IGF-1 levels increased to >1.20 xULN along the follow up (nine 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 somatostatin analog 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 (18). Our results have shown that long-term remission of acromegaly after octreotide-LAR withdrawal is an uncommon, 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 last injection) further decreased to 5% as patients reached 72 weeks of follow up. Those figures are lower than the 18.5-20% remission rates found in other three studies (14-16) and much lower than the 42% reported in one single report (16), but those percentage rates are derived from proportions (5/27, 4/20, 3/16, and 5/12, respectively) obtained from smaller sample sizes when compared to our study. In addition, those figures should not be compared without carefully analyzing differences in inclusion and remission criteria among 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. That is in marked contrast with our study where only 2 of 58 patients (3.4%) had been on similarly long dose intervals, and also with the other three studies where such dose intervals were used in 10-11 % of patients (14, 16) or were not used at all (15). In addition, the inclusion of patients using cabergoline in combination with somatostatin analogs in one of those studies seems inappropriate to characterize remission after somatostatin analogs withdrawal (15).

Another important consideration is the criteria used to define remission in the various studies. Although we have used a normal IGF-1 as the single biochemical remission criterion, we were able to follow all patients who relapsed with IGF-1 between 1.00 and 1.20 xULN, since our protocol allowed those patients to remain off treatment unless clinically indicated, which occurred in only two patients (11%). Had we adopted the criterion IGF-1 <1.20 xULN as did one previous study with a remission rate of 20% (17), we would have ten instead of four patients in remission at week 60,

which would result in a more comparable remission rate of 17%. Finally, a comparison between the 18.5% remission rate observed at ≥12 months in the study using remission criteria of normal IGF-1 in addition to basal GH <2.5 ng/ml and post-glucose GH <1.00 ng/ml (14) with our 7% remission rate at 60 weeks may not be truly different. In effect, those figures are not statistically different (P=0.10, Fisher´s exact test), reflecting overlapping confidence intervals of those two rates. After longer follow ups, however, those two figures became closer, 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 remission at last evaluation as reported by Ronchi, Verruca et al in a recent personal communication by email).

In contrast to our long-term results, analysis of remission in the short-term revealed that 29% of patients had IGF-1 ≤1.00 xULN at 8 weeks of follow up (corresponding to 12 weeks after last octreotide injection), the first evaluation after octreotide withdrawal in our study. Thus, it is likely that an even higher rate could be achieved had the first reevaluation 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 corroborate previous studies (19-24).

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 (14-16). Although we were not able to identify a predictor factor for long-term remission in our study, patients with lower IGF-1 levels (<2.4 xULN) before the introduction of octreotide-LAR treatment did show 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 xULN after somatostatin analogs withdrawal have been considered in remission in some studies (16,17), we also analyzed their clinical and hormonal behavior throughout the follow up. In the short-term, their GH levels, intermediate between patients in remission (IGF-1≤1.00 xULN) and patients

relapsing with IGF-1 >1.20 xULN, were highly predictive of further IGF-1increases to >1.20 xULN as observed in all those patients in the following visits. Accordingly, normal sex and age adjusted IGF-1 level is a better criterion of remission than IGF-1 <1.20 xULN.

In conclusion, our results showing that long-term remission after octreotide withdrawal in acromegaly is a rare and usually unsustainable event 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 gives further support to the strategy of routinely attempting to increase octreotide dose interval in well controlled patients, thus reducing treatment burden to both patients and health systems.

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REFERENCES

1. Freda PU (2002) Somatostatin analogs in acromegaly. J Clin Endocrinol Metab 87(7):3013–3018.

2. Melmed S (2006) Medical progress: acromegaly. N Engl J Med 355(24):2558–2573.

3. Melmed S, Colao A, Barkan A, Molitch M, Grossman AB, Kleinberg D, Clemmons D, Chanson P, Laws E, Schlechte J, Vance ML, Ho K, Giustina A; Acromegaly Consensus Group. Guidelines for acromegaly management: an update. J Clin Endocrinol Metab. 2009 May;94(5):1509-17.

4. Katznelson L, Laws ER Jr, Melmed S, Molitch ME, Murad MH, Utz A, Wass JA; Endocrine Society. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014 Nov;99(11):3933-51.

5. Vieira Neto L, Abucham J, Araujo LA, Boguszewski CL, Bronstein MD, Czepielewski M, Jallad RS, Musolino NR, Naves LA, Ribeiro-Oliveira Júnior A, Vilar L, Faria M dos S, Gadelha MR. [Recommendations of Neuroendocrinology Department from Brazilian Society of Endocrinology and Metabolism for diagnosis and treatment of acromegaly in Brazil]. Arq Bras Endocrinol Metabol. 2011 Mar;55(2):91-105.

6. Ren SG, Ezzat S, Melmed S, Braunstein GD. Somatostatin analog induces insulin-like growth factor binding protein-1 (IGFBP-1) expression in human hepatoma cells. Endocrinology. 1992 Nov;131(5):2479-81.

7. Pokrajac A, Frystyk J, Flyvbjerg A, Trainer PJ. Pituitary-independent effect of octreotide on IGF1 generation. Eur J Endocrinol. 2009 Apr;160(4):543.

8. Theodoropoulou M, Stalla GK. Somatostatin receptors: from signaling to clinical practice. Front Neuroendocrinol. 2013 Aug;34(3):228-52.

9. Andela CD, Biermasz NR, Kaptein AA, Pereira AM, Tiemensma J. More concerns and stronger beliefs about the necessity of medication in patients with acromegaly are associated with negative illness perceptions and impairment in quality of life. Growth Horm IGF Res. 2015 Oct;25(5):219-26.

10. Postma MR, Netea-Maier RT, van den Berg G, Homan J, Sluiter WJ, Wagenmakers MA, van den Bergh AC, Wolffenbuttel BH, Hermus AR, van Beek AP. Quality of life is impaired in association with the need for prolonged postoperative

therapy by somatostatin analogs in patients with acromegaly. Eur J Endocrinol. 2012 Apr;166(4):585-92

11. Passos VQ, Souza JJ, Musolino NR, Bronstein MD. Long-term follow-up of prolactinomas: normoprolactinemia after bromocriptine withdrawal. J Clin Endocrinol Metab. 2002 Aug;87(8):3578-82.

12. Colao A, Di Sarno A, Cappabianca P, Di Somma C, Pivonello R, Lombardi Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. N Engl J Med. 2003 Nov 20;349(21):2023-33.

13. Dekkers OM, Lagro J, Burman P, Jørgensen JO, Romijn JA, Pereira AM. Recurrence of hyperprolactinemia after withdrawal of dopamine agonists: systematic review and meta-analysis. J Clin Endocrinol Metab. 2010 Jan;95(1):43-51.

14. Ronchi CL, Rizzo E, Lania AG, Pivonello R, Grottoli S, Colao A, Ghigo E, Spada A, Arosio M, Beck-Peccoz P. Preliminary data on biochemical remission of acromegaly after somatostatin analogs withdrawal. Eur J Endocrinol. 2008 Jan;158(1):19-25.

15. Hatipoglu E, Bozcan S, Kadioglu P. Discontinuation of somatostatin analogs while acromegaly is in long-term remission. Pituitary. 2015 Aug;18(4):554-60.

16. Vilar L, Fleseriu M, Naves LA, Albuquerque JL, Gadelha PS, dos Santos Faria M, Nascimento GC, Montenegro RM Jr, Montenegro RM. Can we predict long-term remission after somatostatin analog withdrawal in patients with acromegaly? Results from a multicenter prospective trial. Endocrine. 2014 Aug;46(3):577-84.

17. Ramírez C, Vargas G, González B, Grossman A, Rábago J, Sosa E, Espinosa-de-Los-Monteros AL, Mercado M. Discontinuation of octreotide LAR after long term, successful treatment of patients with acromegaly: is it worth trying? Eur J Endocrinol. 2012 Jan;166(1):21-6.

18. Barkan AL. Biochemical markers of acromegaly: GH vs. IGF-I. Growth Horm IGF Res. 2004 Jun;14Suppl A: S97-100.

19. Lorcy Y, Dejager S, Chanson P; French Octreotide LAR Group.Time course of GH and IGF-1 levels following withdrawal of long-acting octreotide in acromegaly. Pituitary. 2000 Nov;3(3):193-7.

20. James RA, Gilroy J. Dose and frequency titration of somatostatin analogues in the treatment of acromegaly - an injection of expediency? Clin Endocrinol (Oxf). 2001 Jan;54(1):11-3.

21. Gilroy JJ, James RA. Optimizing somatostatin analog therapy in acromegaly: long-acting formulations. Treat Endocrinol. 2002;1(3):149-54. Review

22. Biermasz NR, van den Oever NC, Frölich M, Arias AM, Smit JW, Romijn JA, Roelfsema F. Sandostatin LAR in acromegaly: a 6-week injection interval suppresses GH secretion as effectively as a 4-week interval. Clin Endocrinol (Oxf). 2003 Mar;58(3):288-95.

23. Turner HE, Thornton-Jones VA, Wass JA. Systematic dose-extension of octreotide LAR: the importance of individual tailoring of treatment in patients with acromegaly. Clin Endocrinol (Oxf). 2004 Aug;61(2):224-31.

24. Giustina A, Chanson P, Kleinberg D, Bronstein MD, Clemmons DR, Klibanski A, van der Lely AJ, Strasburger CJ, Lamberts SW, Ho KK, Casanueva FF, Melmed S; Acromegaly Consensus Group. Expert consensus document: A consensus on the medical treatment of acromegaly. Nat Rev Endocrinol. 2014 Apr;10(4):243-8.

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

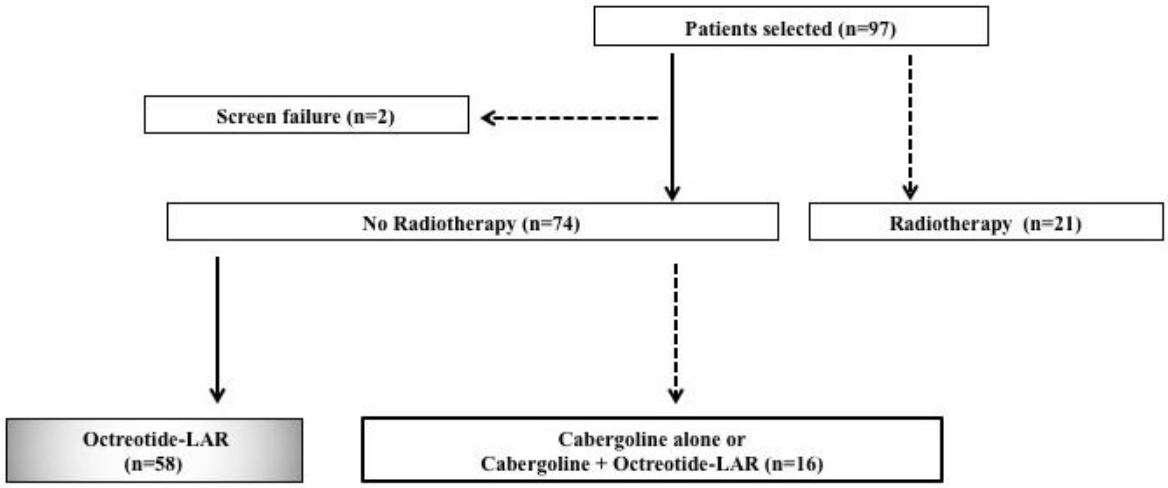

Figure 2. Kaplan-Meier analysis of remission rates (IGF-1 ≤1.00 xULN) after octreotide withdrawal along 72 weeks. Arrows show the probabilities of short and long term remission at the prespecified time points.

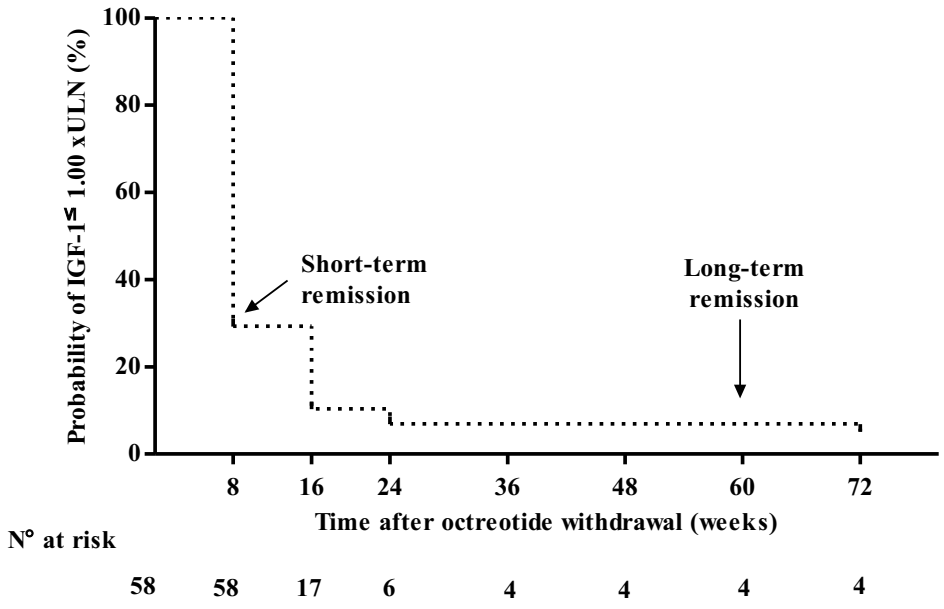

Figure 3. Follow up of IGF-1 serum levels in 18 patients with acromegaly relapsing with IGF-1 between 1.00 and 1.20 xULN after octreotide withdrawal

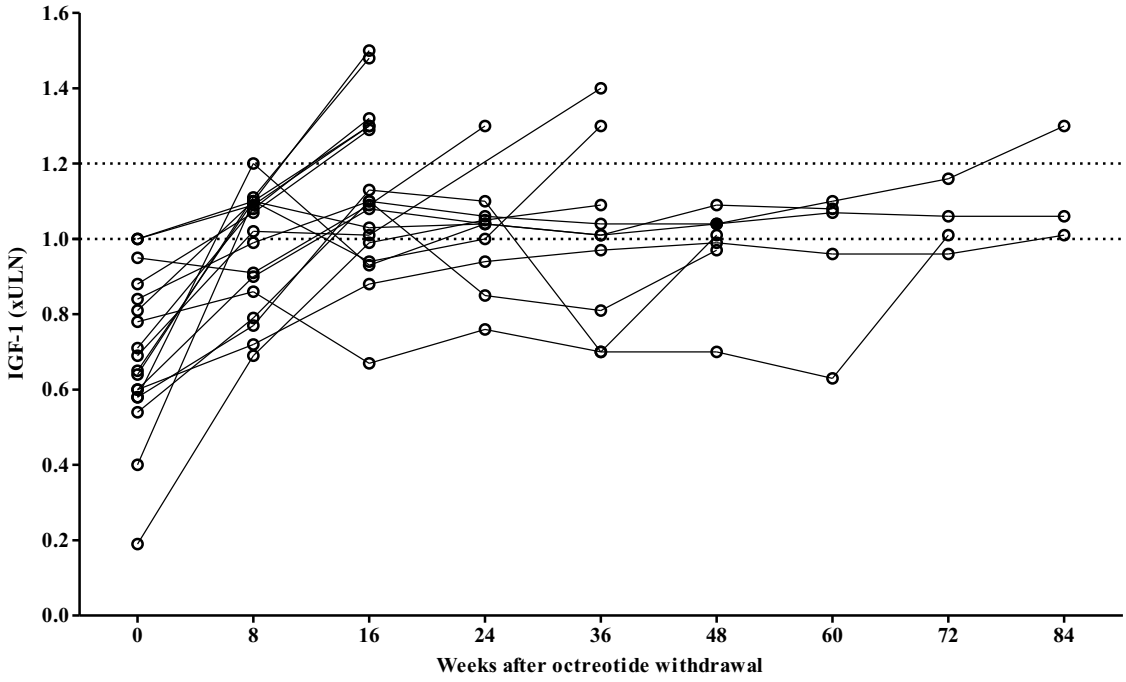

Figure 4. GH levels at 8 weeks after octreotide withdrawal according to IGF-1 serum levels.

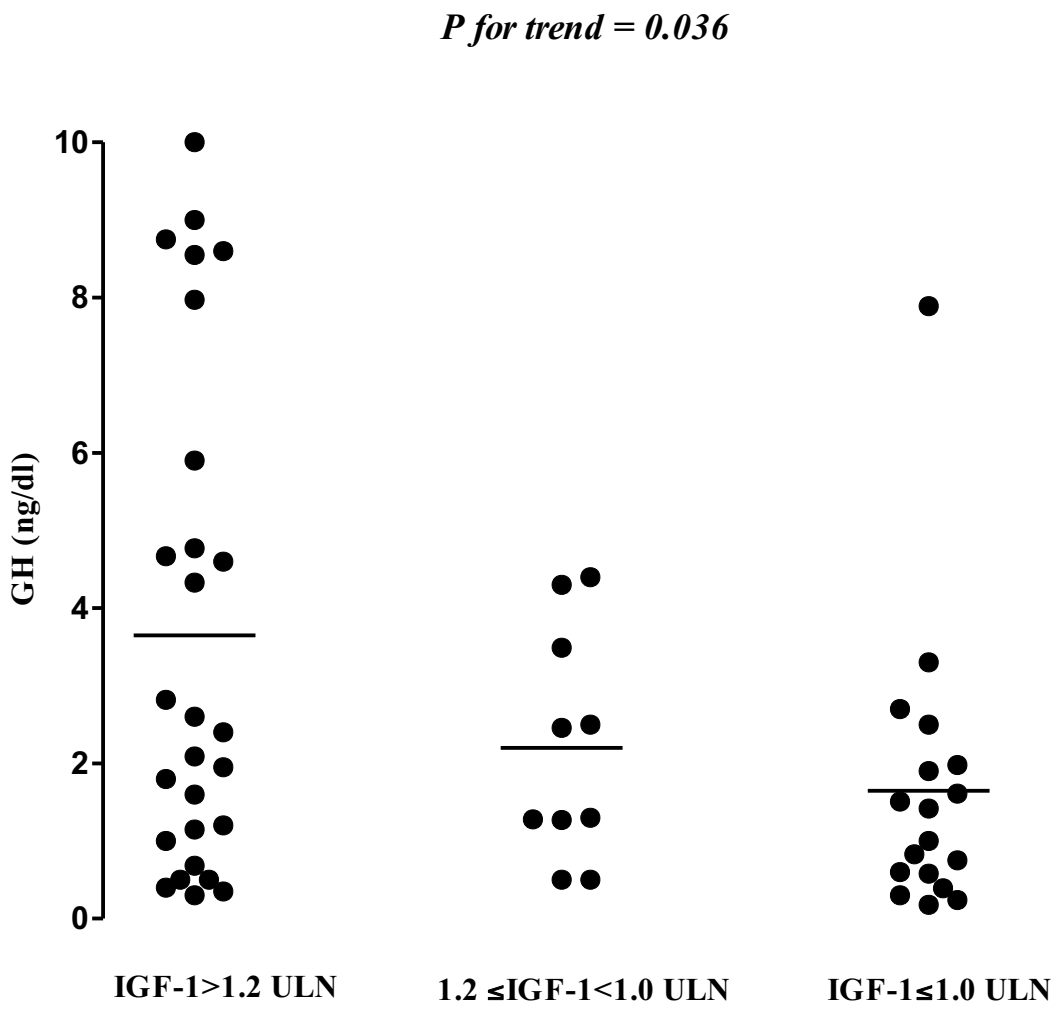

Table 1. Baseline demographic characteristics in 58 well controlled patients with acromegaly

Age at the diagnosis (y)	45 ± 11 (21-71)
Age at study entry (y)	54 ± 11 (27-77)
Female, n (%)	40 (74%)
Macroadenoma, n (%)	54 (93%)
GH levels (ng/ml) at diagnosis	20.3 (1.04-178)
IGF-1 (x ULN) at diagnosis	3.0 (1.4-9.1)
DM2, n (%)	22 (41%)
Hypertension, n (%)	33 (61%)
Previous Surgery, n (%)	46 (85%)
Tumor remnant at study entry, n (%)	27 (50%)
Duration of medical therapy (mo)	49 (24-173)
Octreotide-LAR 10 mg/mo [n (%)]	3 (5%)
Octreotide-LAR 20 mg/mo [n (%)]	34 (59%)
Octreotide-LAR 30 mg/mo [n (%)]	21 (36%)
4-week dose interval [n (%)]	51 (88%)
(4-8)-week dose interval [n (%)]	5 (8.6%)
>8-week dose interval [n (%)]	2 (3.4%)
Mean IGF-1 (xULN) during 24 mo before study	0.8 ± 0.15 (0.28-1.00)
GH levels (ng/ml) at study entry	1.14 ± 1.2 (0.08-5.00)
IGF-1 (xULN) at study entry	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.

Artigo 2

Remission of acromegaly after medical treatment withdrawal can also occur in patients controlled by octreotide and cabergoline or cabergoline alone

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Abbreviated Title: Remission of acromegaly after medical treatment withdrawal

Key terms: acromegaly, combination therapy, remission, somatostatin analog, cabergoline

ABSTRACT

Purpose: Remission of acromegaly has been reported after somatostatin analogs withdrawal, but not after withdrawal of combination therapy with cabergoline, and only sporadically in patients controlled by cabergoline alone.

Methods: To establish the remission rates (normal IGF-1 for age/sex: IGF-1≤1.00 xULN) after withdrawal of combined treatment with octreotide-LAR and cabergoline and cabergoline alone we prospectively studied 16 patients with acromegaly controlled by those treatments in the preceding two years as part of a larger study on remission of acromegaly after withdrawal of different medical treatments.

Results: Among 97 patients with controlled acromegaly included in the entire study, only 16 patients had been on combination therapy (n=12) or cabergoline alone (n=4). At eight weeks after treatment withdrawal, three patients (19%) were in remission (short-term remission). At 60 weeks (long-term remission), IGF-1 levels were still in the normal range in two patients (12.5%) and remained normal up to 108 weeks after treatment withdrawal (last visit). One patient had been treated with cabergoline alone and another one with combination of octreotide and cabergoline before treatment withdrawal. Those two patients represent, respectively, 25% and 8.5% of remission rates according to type of previous treatment.

Conclusion: Remission of acromegaly after withdrawal of treatment can also occur in patients with acromegaly controlled by cabergoline alone or cabergoline combined with octreotide.

INTRODUCTION

Remission of acromegaly after withdrawal of somatostatin analogs has been observed in several prospective studies [1-5]. However, remission after withdrawal of combined treatment with somatostatin analogs and cabergoline has not been previously reported, and remission after withdrawal of treatment with cabergoline alone has been only documented in a single report of two cases [6].

Dopamine agonists, mostly cabergoline, have been successfully used in the treatment of prolactinomas [7] with remission rates after treatment withdrawal of 16% - 21% according to a recent meta-analysis [8]. Cabergoline has also been effectively used in the treatment of acromegaly, either alone, usually in patients with mild increases in IGF-1 levels, or in combination with somatostatin analogs, in patients only partially responsive to those analogs [9, 10].

We have recently conducted a large prospective multicenter study on remission of acromegaly after withdrawal of different pharmacological treatments directed at the pituitary adenoma. Octreotide-LAR withdrawal was shown to be an uncommon and frequently unsustainable event [5], although higher remission rates have been previously reported in relatively smaller studies using variable inclusion and remission criteria [1-4]. In this report, we present data on remission after treatment withdrawal in patients controlled with octreotide and cabergoline or with cabergoline alone that were enrolled in that large prospective multicenter study.

SUBJECTS AND METHODS

Study Overview

We conducted the study from December 13, 2012 through September 30, 2015, at 14 university referral centers for pituitary diseases from10 cities in eight 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. The two investigators from the coordinator site (AC and JA, Escola Paulista de Medicina, Universidade Federal de São Paulo) were responsible for project design, data collection, monitoring, and analysis, and manuscript preparation. All authors reviewed and approved the manuscript before its submission for publication.

Patients

We analyzed all 16 patients with acromegaly controlled by combination therapy with octreotide-LAR and cabergoline or cabergoline alone. Those patients were drawn from a larger population of 97 well- controlled patients after exclusion of screen failures (IGF-1>1.00 xULN at screening visit); patients on octreotide-LAR alone; and patients previously submitted to radiotherapy (Figure 1). All patients met the inclusion criteria: primary or adjuvant medical treatment for ≥24 months, dose and dose interval unchanged in the last 12 months, mean IGF-1 ≤1.00 xULN (patient´s mean IGF-1divided by IGF-1 upper limit for age and sex) in the previous 24 months, and a confirmatory IGF-1 ≤1.00 xULN at the screening visit. 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, 84, 96 and 108 weeks after treatment withdrawal (the first assessment at week 8 corresponds to eight weeks after the last cabergoline dose and 12 weeks after the last octreotide injection). A pituitary MRI was performed between weeks 48 and 60 for patients in remission.

After treatment withdrawal, patients with IGF-1≤1.00 xULN at each visit were considered in remission and continued the study without medication for acromegaly. Patients presenting IGF-1>1.00 xULN during follow up were considered relapses.

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 each eight weeks (short-term remission) and at ≥60 weeks (long-term remission) after drug withdrawal.

Secondary end-points included: 1) clinical activity of disease as judged by the attending physician; 2) biochemical assessments [serum GH, fasting blood glucose, and glycosylated hemoglobin (HbA1c) by routinely available methods]; and 3) 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 of those parameters were evaluated at each visit.

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 kit manufacturer’s information.

Statistical Analyses

Mean, median and standard deviation (SD) were use for descriptive data.

Associations between two categorical variables were calculated by Fisher´s exact test. Data were analyzed using GraphPad Prism 5.0

RESULTS

Among the 14 centers that enrolled patients with acromegaly controlled by different medical treatments in the entire study, four centers included 16 non-irradiated patients controlled by cabergoline, alone or in combination with octreotide-LAR. As shown in Figure 1, most of the patients enrolled in the larger study were treated with octreotide alone and their results were recently reported elsewhere [5].

Among those 16 patients, four patients had been controlled by cabergoline alone (2.0 - 3.5 mg/w) and 12 patients by combined treatment with cabergoline (0.5 - 3.5 mg/w) and octreotide (20-40 mg/mo). Combination treatment was started with octreotide in nine patients and with cabergoline in the remaining three patients. The baseline characteristics of all patients are shown according to previous medical treatment in **Tables 1 and 2**.

Short and long-term remission after treatment withdrawal

Overall, three patients (19%) were in short-term remission (week 8) and two (12.5%) remained in remission at ≥60 weeks (long-term remission) according to serum IGF-1≤1.00 xULN (**Figure 2**). Among the 16 patients included in the study according to the prespecified criterion (normal IGF-1), 11 patients (69%) had GH levels <1.00 ng/mL and 5 (31%) had GH levels above that cut-off (mean:1.36 ng/mL, range: 1.05-2.10 ng/mL) before treatment withdrawal. After treatment withdrawal, GH levels remained <1.00 ng/mL in all or in most measurements during the entire follow up of the two patients in long-term remission (**Figure 3**).

Combination therapy with cabergoline and octreotide-LAR

Table 1 shows the baseline characteristics of the 12 patients controlled with combination therapy.

At week 8, which corresponds to 12 weeks after the last injection of octreotide-LAR and eight weeks after the last dose of cabergoline, only one of 12 patients (8.5%) previously controlled by combination treatment was in remission (short-term remission) and remained so at week 60 (long-term remission) and during the entire follow up (108

weeks). During remission, that patient presented no clinical signs or symptoms of disease activity or tumor growth, and her GH levels, fasting glycaemia, HbA1c levels, and AcroQol scores remained similar to those observed during combined treatment. However, a pituitary MRI at 48 weeks revealed a slight increase in tumor volume.

Cabergoline alone

Table 2 shows the baseline characteristics in the four patients controlled with cabergoline alone.

At week 8, which corresponds to eight weeks after the last dose of cabergoline, two of the four patients controlled by cabergoline alone were in remission (short-term remission) and the remaining two patients had already relapsed; another patient relapsed at week 16.

At week 60, one patient (25%) was still in remission (long-term remission) and remained so during the entire follow up (108 weeks), with no clinical signs or symptoms suggestive of disease activity or tumor growth.

After treatment withdrawal, that patient presented episodes of headache that disappeared at her second follow up visit. Off treatment, she did not show clinical signs or symptoms of disease activity or tumor growth, and her GH levels, fasting glycaemia, HbA1c levels, and AcroQol scores remained similar to those observed during cabergoline treatment. A pituitary MRI at 48 weeks was unchanged, with no visible tumor.

In common, both patients in long-term remission were female; were diagnosed with acromegaly before 40 years old; had macroadenomas with previous surgery; only mildly elevated IGF-1 levels before medical therapy (1.16 and 1.46 xULN); and GH levels ≤ 1.00 ng/mL before treatment withdrawal.

Distinctive features, present only in Patient 8 were: tumor remnant visible at MRI (mostly in the right cavernous sinus), high prolactin levels, and oral estrogen/progesterone replacement therapy (kept unchanged during the entire study). That patient had experienced partial reduction of the tumor during combined treatment with octreotide and cabergoline and presented a non-symptomatic small increase in tumor volume after treatment withdrawal as shown by a MRI at week 48. Her prolactin levels, high at diagnosis (>300 ng/mL), but normal during combined octreotide and cabergoline treatment, progressively increased to 590 ng/mL at week 108, despite

persistently normal IGF-1 levels and GH levels <1.0 ng/mL (mean: 0.75 ng/mL, range: 0.56 - 0.97 ng/mL) during the entire follow up without medical treatment (Figures 2 and 3). Treatment was restarted only with cabergoline at week 108 and successfully decreased tumor volume and prolactin levels

DISCUSSION

In this prospective study, we have shown that patients with acromegaly controlled by combination therapy with octreotide and cabergoline or with cabergoline alone can also achieve remission after treatment withdrawal, as already demonstrated in patients controlled by somatostatin analogs alone [1-5].

The 16 patients with controlled acromegaly using cabergoline alone or combination therapy in this report represent only 22% of the total number of non-irradiated patients enrolled in the large study. The remaining patients were controlled with octreotide alone. This difference may be attributed to several factors including octreotide being the first line medical therapy according to current guidelines, differences in efficacy between medications, and treatment preferences of participating centers [11, 12].

The long-term remission rates according to treatment at week 60 (8.5% after combination treatment withdrawal and 25% after cabergoline withdrawal) are not statistically different from the 7.5% after octreotide withdrawal in our previous report using the same protocol. However, after longer follow ups, remission was sustained in both patients in this study (108 weeks off treatment), but not always in patients treated with octreotide alone, which declined to 5% at week 72 and to≤3.4% at week 108 [5]. Due to the relatively small number of patients and paucity of remission events in these studies, one cannot draw definite conclusions about the true remission rates, and future studies with much larger number of patients and more statistical power should reduce that uncertainty.

Interestingly, both patients in long-term remission after cabergoline or cabergoline and octreotide withdrawal had pre-medical treatment IGF-1 levels that were only mildly elevated. This finding was also observed in all four patients in long-term remission (60 weeks) after octreotide treatment withdrawal in our previous report [5]. These observations could suggest that the probability of remission of acromegaly after treatment withdrawal may be related to mildly elevated IGF-1 levels before medical treatment rather than to the medical treatment used to achieve IGF-1 control. However, more studies with larger samples and future meta-analysis are necessary to

definitely establish pre-treatment IGF-1 levels as a predictive factor of remission after medical treatment withdrawal in acromegaly.

REFERENCES

1. Ronchi CL, Rizzo E, Lania AG, Pivonello R, Grottoli S, Colao A, Ghigo E, Spada A, Arosio M, Beck-Peccoz P Preliminary data on biochemical remission of acromegaly after somatostatin analogs withdrawal. Eur J Endocrinol 158(1):19-25 (2008)
2. Ramírez C, Vargas G, González B, Grossman A, Rábago J, Sosa E, Espinosa-de-Los-Monteros AL, Mercado M: Discontinuation of octreotide LAR after long term, successful treatment of patients with acromegaly: is it worth trying? Eur J Endocrinol 166(1):21-6 (2012)
3. Vilar L, Fleseriu M, Naves LA, Albuquerque JL, Gadelha PS, dos Santos Faria M, Nascimento GC, Montenegro RM Jr, Montenegro RM Can we predict long-term remission after somatostatin analog withdrawal in patients with acromegaly? Results from a multicenter prospective trial. Endocrine 46(3):577-84 (2014)
4. Hatipoglu E, Bozcan S, Kadioglu P: Discontinuation of somatostatin analogs while acromegaly is in long-term remission. Pituitary 18(4):554-60 (2015)
5. Casagrande A, Bronstein MD, Jallad RS, Moraes AB, Elias P C.L, Castro M, Czepielewski MA, Boschi A, Oliveira Jr AR, Schweizer JROL, Vilar L, Nazato DM, Gadelha MR, Abucham J; at al. Long-term remission of acromegaly after octreotide withdrawal is an uncommon and frequently unsustainable event. Neuroendocrinology, in review (2016)
6. Verhelst JA, Abrams PJ, Abs R: Remission of acromegaly following long-term therapy with cabergoline: report of two cases. Pituitary 11(1):103-7 (2008)
7. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA; Endocrine Society. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 96(2):273-88 (2011)
8. Dekkers OM, Lagro J, Burman P, Jørgensen JO, Romijn JA, Pereira AM Recurrence of hyperprolactinemia after withdrawal of dopamine agonists: systematic review and meta-analysis. J Clin Endocrinol Metab 95(1):43-51 (2010)
9. Mattar P, Alves Martins MR, Abucham J: Short- and long-term efficacy of combined cabergoline and octreotide treatment in controlling IGF-I levels in acromegaly. Neuroendocrinology 92(2):120-7 (2010)

10. Sandret L, Maison P, Chanson P: Place of cabergoline in acromegaly: a meta-analysis. J Clin Endocrinol Metab 96(5):1327-35 (2011)
11. Melmed S, Colao A, Barkan A, Molitch M, Grossman AB, Kleinberg D, Clemmons D, Chanson P, Laws E, Schlechte J, Vance ML, Ho K, Giustina A: Acromegaly Consensus Group. Guidelines for acromegaly management: an update. J Clin Endocrinol Metab 94(5):1509-17 (2009)
12. Giustina A, Chanson P, Kleinberg D, Bronstein MD, Clemmons DR, Klibanski A, van der Lely AJ, Strasburger CJ, Lamberts SW, Ho KK, Casanueva FF, Melmed S: Acromegaly Consensus Group. Expert consensus document: A consensus on the medical treatment of acromegaly. Nat Rev Endocrinol 10(4): 243-8 (2014)

Figure 1. Flow chart of the entire study population

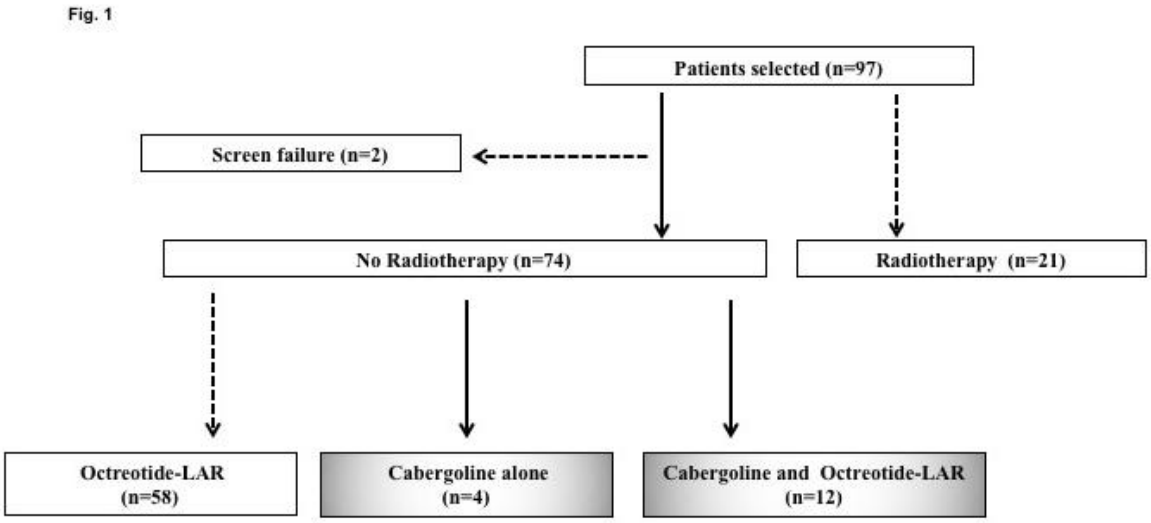

Figure 2. IGF-1 levels in 16 patients with acromegaly before and after treatment withdrawal

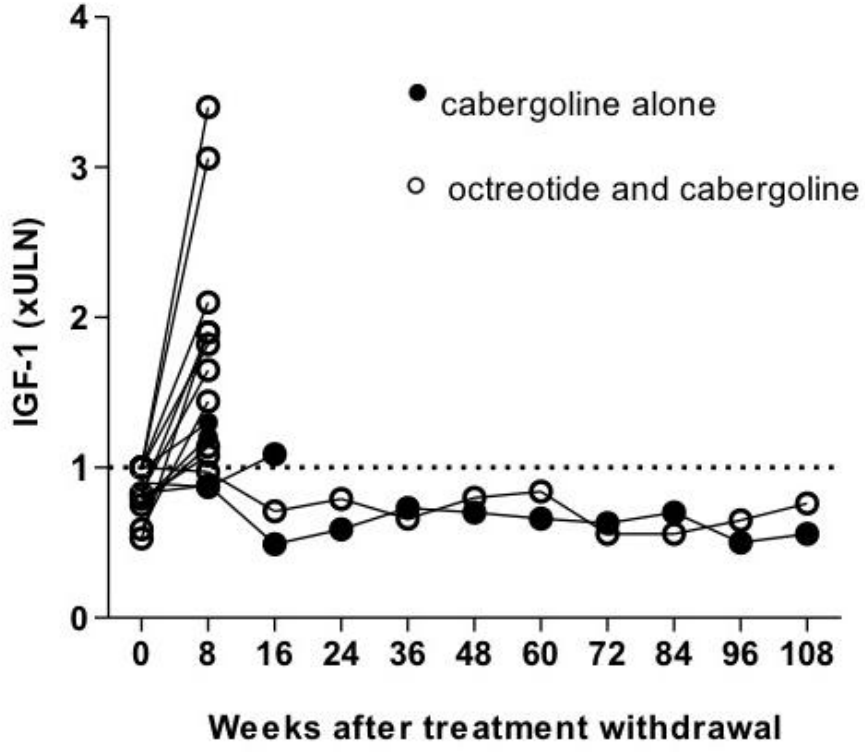

Figure 3. GH levels in 16 patients with acromegaly before and after treatment withdrawal

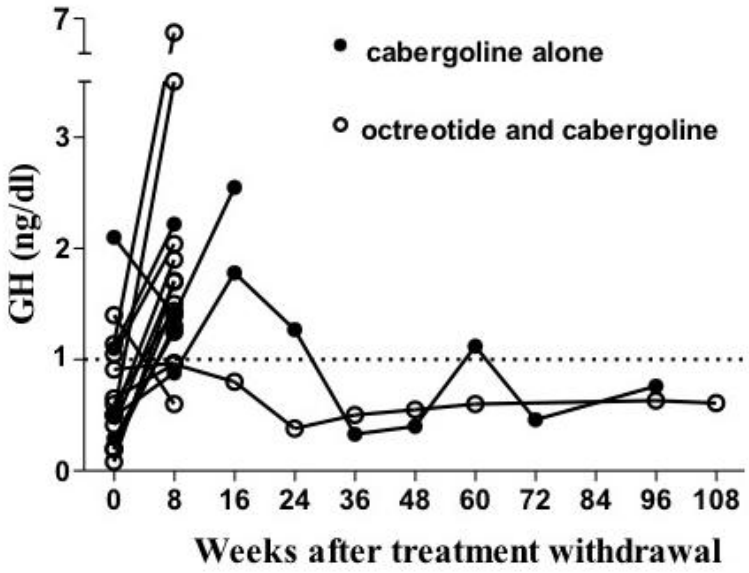

Table 1. Baseline characteristics in patients with acromegaly controlled by cabergoline and octreotide

Patient	Sex	Age (y)	PRL at diagnosis (ng/mL)	Previous Surgery	Tumor IHC	Visible Tumor at MRI	GH before medical treatment (ng/mL)	IGF-1 before medical treatment (xULN)	Octreotide Dose (mg/mo)	Cabergoline Dose (mg/w)	Duration of medical treatment (mo)	GH at study entry (ng/mL)	IGF-1 at study entry (xULN)
5	M	62	52	Y	GH and PRL	Y	16	1.76	30	3.5	68	0.91	0.84
6	F	60	13	Y	GH and PRL	N	2.5	1.70	30	2.0	28	0.08	0.59
7	M	41	15	Y	GH and PRL	Y	1.1	2.34	30	1.0	52	0.19	1.00
8	**F**	**26**	**303**	**Y**	**GH and PRL**	**Y**	**8**	**1.46**	**40**	**3.5**	**60**	**0.65**	**1.00**
9	F	52	57	Y	GH and PRL	Y	2.3	1.46	30	3.5	77	0.50	0.79
10	F	58	NA	N	-----	N	5.6	3.04	20	3.5	30	0.50	1.00
11	F	26	149	Y	GH and PRL	N	NA	2.83	30	1.5	39	0.20	1.00
12	F	55	NA	Y	NA	Y	7.2	NA	30	3.5	42	1.10	1.00
13	M	65	590	N	-----	Y	8.3	4.0	20	3.5	29	1.40	0.82
14	F	51	26	N	-----	Y	3.1	4.1	30	3.5	27	0.60	0.53
15	F	27	NA	Y	GH	N	2.8	1.41	30	1.5	70	1.05	0.75
16	F	76	5.5	N	-----	N	4.3	NA	20	0.5	60	0.41	0.94

PRL prolactin IHC immunohistochemistry; NA not available. Line in bold represents the patient in remission.

Table 2. Baseline characteristics of patients controlled by cabergoline alone

Patient	Sex	Age	PRL at diagnosis (ng/mL)	Previous Surgery	Tumor IHC	Visible tumor at MRI	GH before medical treatment (ng/mL)	IGF-1 before medical treatment (xULN)	Cabergoline Dose (mg/w)	Duration of medical treatment (mo)	GH at study entry (ng/mL)	IGF-1 at study entry (xULN)
1	F	26	87	Y	GH and PRL	N	1.6	1.09	2.0	46	1.09	0.77
2	F	54	NA	Y	NA	N	2.8	2.12	2.5	36	0.29	0.99
3	**F**	**42**	**26**	**Y**	**GH and PRL**	**N**	**1.6**	**1.16**	**3.5**	**29**	**0.49**	**0.83**
4	M	70	NA	N	-	Y	NA	NA	3.5	56	2.10	0.90

PRL prolactin; IHC immunohistochemistry; NA not available. Line in bold represents the patient in remission.

Anexo

PROJETO: REMISSÃO DA ACROMEGALIA APÓS SUSPENSÃO DO TRATAMENTO FARMACOLÓGICO: ESTUDO PROSPECTIVO MULTICÊNTRICO.

Investigador principal: Julio Abucham

Investigadores associados convidados: Alessandra Casagrande, Aline B. Moraes, Ana Tabet, Ana B.W. Tavares, Antonio Ribeiro-Oliveira Jr, Artur Boschi, Carolina G.S. Leães, Cesar L. Boguszewski, Débora M. Nazato, Estela M. Jatene, Jose I. Mota, Junia R.O.L Schweizer, Lucio Vilar, Marcello D. Bronstein, Margaret de Castro, Mauro A Czepielewski, Monica R. Gadelha, Nina Musolino, Nilza Scalissi, Paula C.L. Elias, Paulo A.C. Miranda, Raquel S. Jallad, Vania S. Nunes

I) INTRODUÇÃO

A acromegalia é uma doença crônica e debilitante que resulta da exposição sustentada a níveis elevados do hormônio do crescimento (GH) e do fator de crescimento dependente de GH ou IGF-1. Em cerca de 98% dos casos, a hipersecreção de GH provém de um adenoma hipofisário (1).

O tratamento convencional da acromegalia visa reduzir a secreção tumoral de GH e normalizar os níveis de GH e IGF-1, bem como controlar os efeitos de massa do adenoma (2). Em geral, o tratamento envolve cirurgia, medicamentos e radioterapia, isoladamente ou, mais freqüentemente, em associação. A maioria dos pacientes acromegálicos requer uma combinação terapêutica para atingir os alvos laboratoriais de controle hormonal (GH e/ou IGF-1) e controle do crescimento tumoral (3).

As drogas mais utilizadas no tratamento da acromegalia são a octreotida, um análogo sintético da somatostatina, com eficácia no controle hormonal em cerca de 50% dos casos, e a cabergolina, um análogo dopaminérgico, cuja eficácia é inferior a 40%. A combinação de cabergolina e octreotida pode ser eficaz em até 40% dos pacientes não controlados apenas com octreotida (4, 5, 6).

A freqüência de remissão hormonal após suspensão do tratamento farmacológico com agonistas dopaminérgicos em tumores hipofisários secretores de prolactina prolactinomas) está bem estabelecida e pode ser relativamente alta (7,8). Na acromegalia, a remissão após suspensão do tratamento farmacológico tem sido freqüentemente observada em pacientes previamente submetidos à radioterapia. Em pacientes não irradiados, contudo, os estudos são poucos e o número de pacientes analisados tem sido relativamente pequeno para se estabelecer a real prevalência e os fatores prognósticos para a remissão após tratamento farmacológico.

Em um dos dois únicos estudos prospectivos publicados até o presente, a taxa de remissão após suspensão da octreotida foi de 42% em pacientes previamente operados e acompanhados por 12 a 18 meses após suspensão. Nesse estudo, os pacientes foram pré-selecionados por tratamento estável, tempo mínimo de controle, controle hormonal mantido com doses em intervalos crescentes e remanescente tumoral pequeno ou não visível (9). No outro estudo, a taxa de remissão foi de 18%, em seguimento de 12 a 48 meses após suspensão da octreotida, sendo que os

pacientes foram pré-selecionados por tempo de tratamento (>12 meses) e ausência de crescimento tumoral (10).

Assim, é preciso que estudos prospectivos mais abrangentes e com maior número de pacientes sejam conduzidos para se estabelecer a freqüência e o tempo de remissão após suspensão e possíveis fatores preditivos. Esses estudos deverão contribuir para o estabelecimento de orientações para suspensão ou redução da medicação ao longo do tempo, o que trará benefícios para os pacientes bem como significativa redução do custo do tratamento.

II) **OBJETIVOS**

1) Avaliar a freqüência de remissão hormonal da acromegalia após a retirada de tratamento farmacológico com octreotida e/ou cabergolina em pacientes cronicamente controlados, seja em tratamento primário ou adjuvante.

2) Em casos de recidiva “tardia” (após 16 semanas ou mais da suspensão do tratamento farmacológico), avaliar a freqüência de controle hormonal com doses menores (se cabergolina) ou intervalos maiores entre doses (se octreotida).

3) Avaliar a variação do volume tumoral após a suspensão do tratamento farmacológico.

4) Identificar possíveis fatores prognósticos para a remissão ou para redução de dose presentes antes ou durante o tratamento farmacológico.

5) Analisar o impacto da suspensão e da redução desses medicamentos sobre o custo financeiro do tratamento.

III) **DURAÇÃO DO ESTUDO**

O estudo terá um período de 24 semanas para inclusão dos pacientes. A duração de cada paciente no estudo será variável, entre 8 e 108 semanas, a depender do resultado individual.

IV) **DESFECHOS**

1) Proporção de pacientes que permaneceram com IGF-1 ≤ 1,20 (limite superior da normalidade para a idade) xLSN a cada visita após suspensão do tratamento medicamentoso.

2) Proporção de pacientes que, após reintrodução da medicação por recidiva hormonal, mantiveram IGF-1 ≤ 1,20 LSN utilizando um intervalo de tempo maior entre as aplicações de octreotida (em relação ao intervalo antes da suspensão) ou uma dose menor de cabergolina (em relação à dose utilizada antes da suspensão).

3) Variação do volume tumoral após suspensão do tratamento farmacológico.

4) Custo financeiro do controle hormonal antes e após suspensão ou redução da medicação.

V) **PACIENTES**

Serão estudados pacientes portadores de acromegalia em acompanhamento regular no ambulatório de Endocrinologia da Unifesp, o qual será o centro coordenador do estudo, e em outros centros especializados do Brasil (Universidade Federal de São Paulo/Escola Paulista de Medicina; SEMPR, Universidade Federal do Paraná; Hospital das Clinicas da FMUSP, Faculdade de Medicina da USP; Faculdade de Medicina de Ribeirão Preto/USP; Hospital de Clínicas de Porto Alegre, Faculdade de Medicina da UFRGS; Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro; Faculdade de Medicina da UFC, Fortaleza; Instituto de Psiquiatria do Hospital das Clinicas da FMUSP; Santa Casa de Misericórdia de Belo Horizonte; Hospital Geral de Fortaleza/SUS; Universidade Federal de Pernambuco (Hospital das Clinicas Da UFPE); Faculdade de Medicina (UFMG), Universidade

Federal de Goiás (Hospital Das Clinicas da UFG); Universidade Federal de Ciências da Saúde de Porto Alegre; Escola de Medicina de Botucatu, Universidade do Estado

de são Paulo; Santa Casa de Misericórdia de São Paulo; Universidade do Estado do Rio de Janeiro, após consentimento livre e esclarecido.

Número de pacientes: 80

Número de centros participantes: 16

VI) **CRITÉRIOS DE INCLUSÃO**

Tratamento da acromegalia, primário ou adjuvante (após cirurgia), com octreotida e/ou cabergolina por ≥ 24 meses.

Controle hormonal (média de todas as dosagens de IGF-1≤ 1.0 LSN durante os últimos 24 meses de tratamento com um mínimo de 2 dosagens, sendo pelo menos uma nos últimos 12 meses).

Dose de medicamento e/ou intervalo entre doses sem mudanças há pelo menos 12 meses.

VII) **CRITÉRIOS DE EXCLUSÃO**

Lesão tumoral distante do quiasma óptico a menos de 5 mm na ressonância magnética de sela turca obtida antes de entrar no estudo.

Radioterapia da região hipofisária nos últimos 10 anos.

Uso de Pegvisomanto.

Não consentimento.

VIII) **CRITÉRIOS PARA RETIRADA DO PACIENTE DO ESTUDO**

Retirada do consentimento.

Perda de follow-up.

Se IGF-1 pré-suspensão (1ª dosagem do estudo na visita de screening) for >1.20 LSN.

IX) **NUMERAÇÃO DO PACIENTE**

Cada paciente será identificado no estudo por um Número do Paciente com 3 dígitos. O Número do Paciente (exemplo: 112) consiste de um Número do Centro (Número do Centro: 1 a 14) seguido de um número (dois dígitos) atribuído conforme a ordem de entrada no estudo naquele centro (01, 02, 03, 12, etc), para que cada paciente tenha um número único no banco de dados. Depois de atribuído, esse

número de paciente não deverá ser reutilizado por nenhum outro paciente e não deverá ser alterado, mesmo se o paciente sair do estudo.

X) **DESENHO DO ESTUDO**:

Todos os pacientes que preencherem os critérios de inclusão e que não tiverem sido retirados por algum dos critérios previamente descritos serão regularmente avaliados através de exame clínico, dosagens hormonais, bioquímicas, nos seguintes tempos:

1) Antes da suspensão da medicação (± 1 semana) e a cada 8 semanas (± 1 semana) após a suspensão durante as primeiras 24 semanas.

2) Após 24 semanas, os pacientes serão avaliados em intervalos de 12 (± 2) semanas até 96-108 semanas.

3) O questionário AcroQoL será aplicado antes e após a suspensão da droga, em todas as visitas.

4) Após 48 semanas (± 8 semanas) e após 96-108 semanas (± 12 semanas), todos pacientes ainda em remissão (sem medicação) serão submetidos à RM de sela turca.

5) Em pacientes com queixa de alteração visual compatível com expansão tumoral ou em pacientes com recorrência tardia (após 16 semanas ou mais), a RM de sela turca deverá ser realizada prontamente.

X.1) **As medicações para acromegalia serão suspensas da seguinte maneira:**

1) Pacientes em monoterapia com octreotida, a data da suspensão é contada a partir da data que seria a da aplicação de octreotida.

2) Pacientes em monoterapia com cabergolina, a data da suspensão é contada 1 dia após a última dose de cabergolina.

3) No tratamento combinado, a cabergolina é suspensa na data que seria a da aplicação da octreotida e essa é a data da suspensão do tratamento.

X.2) **Critérios para manter suspensão e critérios para reintroduzir medicação durante o seguimento:**

1)Todos pacientes com IGF-1 ≤1.20 LSN deverão continuar no estudo sem medicação.

2) Caso ocorra elevação de IGF-1 > 1.20 LSN, a medicação deverá ser reintroduzida na (s) mesma (s) dose (s) e intervalos utilizados imediatamente antes da suspensão.

3) Nos pacientes com recorrência precoce (já na primeira dosagem de IGF-1 após suspensão), o tratamento será reintroduzido (Cf item 2 acima) e o paciente será descontinuado do estudo.

4) Nos pacientes com recorrência tardia (além da primeira avaliação pós-suspensão: ≥16 semanas), o tratamento será reintroduzido (cf item 2) e será mantido até atingir IGF-1≤1.0 LSN, após o que a medicação deverá ser reajustada da seguinte forma:

(a) Só octreotida: mesma dose/aplicação e acréscimo de +2 semanas ao intervalo entre doses, com possibilidade de novo ajuste após 4 aplicações conforme IGF-1 antes da 4ª aplicação, a saber,

IGF-1<1.00 LSN: aumentar intervalo em +2 semanas;

IGF-1 entre 1.00 e 1.20 LSN: manter intervalo de aplicação;

IGF-1 > 1.20 LSN: retornar ao intervalo entre doses anterior.

(b) Só cabergolina: redução da dose semanal para aproximadamente a metade (de 7 cps para 4 cps; de 6 ou 5 cps para 3 cps; de 4 ou 3 cps para 2 cps; de 2 cps para 1 cp; de 1 cp para ½ cp), com possibilidade de novo ajuste seguindo a mesma fórmula conforme IGF-1 após um período de tratamento ≥8 semanas, a saber:

IGF-1<1.00 LSN: reduzir dose.

IGF-1 entre 1.00 e 1.20 LSN: manter dose.

IGF-1 > 1.20 LSN: retornar à dose anterior.

(c) Octreotida + cabergolina: mesma dose/aplicação e acréscimo de +2 semanas ao intervalo entre doses de octreotida, mantendo-se a mesma dose de cabergolina, com possibilidade de novo ajuste após 4 aplicações conforme IGF-1 antes da 4ª aplicação, a saber,

IGF-1<1.00 LSN: aumentar intervalo em +2 semanas;

IGF-1 entre 1.00 e 1.20 LSN: manter intervalo de aplicação;

IGF-1 > 1.20 LSN: retorno ao intervalo entre doses anterio

XI) **MEDICAÇÕES CONCOMITANTES**

Mulheres em uso de contraceptivo ou terapia de reposição com estrogênio oral deverão manter a terapia na mesma dose e via de administração até o final/saída do estudo.

XII) **EXAMES LABORATORIAIS**

Dosagens séricas serão realizadas nos respectivos centros onde os pacientes estão sendo acompanhados.

Coleta de sangue em jejum, pela manhã. Alíquotas extras de soro (± 5 ml) deverão ser estocadas apropriadamente (-20º a -80º C) para futuras dosagens não previstas.

Dosagens e métodos:

1. IGF-1: será dosado em toda visita,

2. GH: será dosado no tempo basal em toda visita

3. TTOG para GH: O primeiro teste de supressão do GH (0-30-60-90-120 min) após glicose oral (75 g) será realizado ainda durante o tratamento, entre 3 e 4 semanas após a última dose de octreotida e antes da suspensão da cabergolina (1-7 dias antes).

O teste de supressão do GH será repetido apenas nos pacientes que se mantiverem sem medicação após 48 semanas de suspensão. O GH e a glicemia deverão ser dosados em todos os tempos do teste. Pacientes com glicemia de jejum > 126 mg/dl não serão submetidos ao teste.

4. Outros: prolactina, T4 livre, T3, TSH, Glicemia de jejum, HbA1C, colesterol total e frações, triglicérides serão dosados em todas as visitas.

5. US de abdômen superior: deverá ser realizado apenas nos pacientes em uso de octreotida, antes da suspensão do medicamento (-16 a +4 semanas da última aplicação).

XIII) **ANÁLISE ESTATÍSTICA**

Cálculo da amostra: admitindo-se uma taxa de remissão em torno de 20% (intervalo de confiança entre 13-30%), o cálculo amostral seria de 80 pacientes em monoterapia com octreotida.

Nível de significância: $P<0,05$ (bicaudal).

Comparações: teste t, teste exato de Fischer,

XIV) **REVISÃO E GERENCIAMENTO DOS DADOS**

O investigador de cada centro deve manter os documentos-fonte para cada paciente no estudo, consistindo em anotações em prontuários, contendo informações demográficas e médicas, dados laboratoriais e os resultados de quaisquer outros exames ou avaliações. O investigador também deve guardar o termo de consentimento livre e esclarecido original assinado pelo paciente (uma cópia assinada é entregue ao paciente).

O investigador associado ou pessoa designada pelo investigador deve inserir as informações dos pacientes participantes no estudo em banco de dados padrão do Excel, aplicável para todos os centros, conforme enviado por email. Em seguida, os dados inseridos deverão ser enviados sistematicamente após cada visita (até 1 mês após) ao centro coordenador. O investigador (ou seu designado) responderá/resolverá qualquer questionamento que venha a ocorrer.

XV) **CRONOGRAMA DAS VISITAS**

visita	VS	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Semana[1]	0	8	16	24	36	48	60	72	84	96	108
TCLE	X										
Criterios inclusao exclusao	X										
Ultima dose medicação[2]	X										
Historia medica	X										
Exame fisico	X	X	X	X	X	X	X	X	X	X	X
Acro QoL	X	X	X	X	X	X	X	X	X	X	X
Medicaçao concomitante	X	X	X	X	X	X	X	X	X	X	X
GH/IGF-1	X	X	X	X	X	X	X	X	X	X	X
PRL, TSH, T4L, T3, glicemia, HbA1c, perfil lipidico	X	X	X	X	X	X	X	X	X	X	X
TTOG para GH[3]	X					X					X
US abdomen superior[4, 5]	X										
RM sela turcica[6,7]	X					X					X

[1] janela de visitas das semanas 0-16: ± 1 semana; das semanas 24-108: ± 2 semanas

[2] anotar medicação, dose e freqüência de administração

[3] O primeiro TTOG deverá ser realizado de 0-7 dias antes da aplicação da octreotida e só será repetido nos pacientes que permanecerem em remissão sem medicação. Pacientes com glicemia de jejum > 126 mg/dl não serão submetidos ao teste

[4] apenas em pacientes em uso de octreotida

[5] deverá ser realizado de -16 a + 4 semanas da última aplicação da octreotida

[6]janela da RM de ± 8 semanas

[7] em pacientes com queixa de alteração visual compatível com expansão tumoral recente ou em pacientes com recorrência tardia, uma RM deverá ser realizada por ocasião desses evento

XIV) **POLÍTICA DE PUBLICAÇÃO**

Qualquer apresentação ou publicação formal dos dados deste estudo serão considerados como publicação conjunta pelos investigadores. A autoria será determinada por acordo mútuo, com base no número de pacientes incluídos. Os investigadores que participarem do estudo concordam em não apresentar dados de um centro ou pequenos grupos de centros antes da publicação completa, ao menos que seja aprovado formalmente por todos os investigadores.

XV) **BIBILIOGRAFIA**

1.Medical progress: Acromegaly. Melmed S. N Engl J Med 2007 Feb 22;356(8):879.

2.Guidelines for acromegaly management: an update. Melmed S, Colao A, Barkan A, Molitch M, Grossman AB, Kleinberg D, Clemmons D, Chanson P, Laws E, Schlechte J, Vance ML, Ho K, Giustina A; Acromegaly Consensus Group. J Clin Endocrinol Metab. 2009 May;94(5):1509-17.

3.Current management practices for acromegaly: an international survey. Giustina A, Bronstein MD, Casanueva FF, Chanson P, Ghigo E, Ho KK, Klibanski A, Lamberts S, Trainer P, Melmed S. Pituitary. 2011 Jun;14(2):125-33.

4. A critical analysis of clinically available somatostatin analog formulations for therapy of acromegaly. Murray RD, Melmed S. J Clin Endocrinol Metab. 2008 Aug;93(8):2957-68. Epub 2008 May 13.

5. Optimizing medical therapy of acromegaly: beneficial effects of cabergoline in patients uncontrolled with long-acting release octreotide. Jallad RS, Bronstein MD.Neuroendocrinology. 2009;90(1):82-92.

6. Short- and long-term efficacy of combined cabergoline and octreotide treatment in controlling igf-I levels in acromegaly. Mattar P, Alves Martins MR, Abucham J. Neuroendocrinology. 2010;92(2):120-7.

7.Predictors of remission of hyperprolactinaemia after long-term withdrawal of cabergoline therapy. Colao A, Di Sarno A, Guerra E, Pivonello R, Cappabianca P, Caranci F, Elefante A, Cavallo LM, Briganti F, Cirillo S, Lombardi G. Clin Endocrinol (Oxf). 2007 Sep;67(3):426-33.

8.Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. Colao A, Di Sarno A, Cappabianca P, Di Somma C, Pivonello R, Lombardi G.N Engl J Med. 2003 Nov 20;349(21):2023-33.

9.Discontinuation of octreotide LAR after long term, successful treatment of patients with acromegaly: is it worth trying? Ramírez C, Vargas G, González B, Grossman A, Rábago J, Sosa E, Espinosa-de-Los-Monteros AL, Mercado M. Eur J Endocrinol. 2012 Jan;166(1):21-6.

10.Preliminary data on biochemical remission of acromegaly after somatostatin analogs withdrawal. Ronchi CL, Rizzo E, Lania AG, Pivonello R, Grottoli S, Colao A,

Ghigo E, Spada A, Arosio M, Beck-Peccoz P. Eur J Endocrinol. 2008 Jan;158(1):19-25.