Clomiphene Citrate for Treatment of Acromegaly Not Controlled by Conventional Therapies

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Context: Oral estrogens, alone or in combination with somatostatin receptor ligands, have been shown to control acromegaly in women. Selective estrogen receptor modulators resulted in similar effects in both genders. Clomiphene citrate (CC), a selective estrogen receptor modulator that increases LH and FSH secretion, improves hypogonadism and fertility outcomes.

Objective: To assess the impact of CC on serum IGF-1 and T levels in male acromegalic patients not controlled by surgery, radiotherapy, and/or medical treatment.

Study Design: In this prospective, open-label, single-center trial, CC (50 mg/d) was added to previous medical treatment for 3 months. Hormonal assessment was performed before and during the intervention.

Patients: Sixteen male patients (median age, 52.8 y; range, 36–79 y) met the following criteria: IGF-1 above the upper limit of normal range for at least 1 year despite the use of available medical therapies, and T levels within or below the third inferior tertile of normality.

Results: Serum IGF-1 levels decreased by 41% (mean ± SD, 424 ± 108 to 250 ± 83 ng/mL; $P < .0004$), leading 44% (seven of 16) of the patients to achieve normal IGF-1 levels. Total serum T levels increased by 209% (282 ± 201 to 497 ± 310 ng/dL), reaching normal levels in 67% (four of six) of those patients considered hypogonadal.

Conclusions: Addition of CC should be considered an option in male acromegaly patients not controlled by current available options, with a considerable cost-saving benefit. Furthermore, improvement of T levels can be obtained in those patients with concurrent central hypogonadism. **(*J Clin Endocrinol Metab* 100: 1863–1869, 2015)**

Despite the many modalities available to treat acromegaly, such as surgery, medical treatment, and radiotherapy, uncontrolled disease persists in a significant portion of patients (1). Several reasons account for this outcome: 1) the presence of large tumors, especially those with cavernous sinus invasion, leading to incomplete tumor resection; 2) the absence of receptors to somatostatin receptor ligands (SRLs) or dopamine agonists (DAs); and 3) the high cost of medications leading to restrictions of their use in many centers.

The role of estrogens in reducing IGF-1 generation in GH-deficient patients under GH replacement is well known. Women of fertile age usually need higher doses of GH to achieve a similar IGF-1 response when compared to men.

Concerning acromegaly, estrogens were used in the past as a treatment option (2). Oral estrogens alone or in combination with SRLs have been shown to control acromegaly in women with mild IGF-1 elevations (3); however, side effects caused by high dosage and the obvious limitation for its use in men sidelined the prescription of these hormones. In the last two decades, selective estrogen receptor modulators (SERMs), drugs that have estrogenic effect in some organs and antiestrogenic effect in others,

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Abbreviations: CAB, cabergoline; CC, clomiphene citrate; DA, dopamine agonist; Oct-LAR, octreotide LAR; SERM, selective estrogen receptor modulator; SRL, somatostatin receptor ligand; STAT, signal transducers and activators of transcription; xULNR, times above upper limit of the normal range.

Table 1. Patients' Characteristics and Drugs in Use During Treatment

Patient No.	Age, y	Pre GH, ng/mL	Post GH, ng/mL	Pre IGF-1, ng/mL	Pre xULNR	Post IGF-1, ng/mL	Post xULNR	3m P/WD IGF-1, ng/mL	3m P/WD xULNR	Medical Treatment	Previous Surgery	Previous Radiotherapy
1	61	2.0	0.5	484	2.34	249	1.20	309	1.49	OCT 30 mg + CAB 3.5 mg	Yes	No
2	53	0.5	0.8	621	2.67	397	1.70	580	2.80	OTC 30 mg	Yes	Yes
3	36	2.0	2.0	550	1.99	437	1.58	541	2.61	OCT 30 mg + CAB 3.5 mg	Yes	No
4	42	1.4	1.4	384	1.47	270	1.03	453	2.19	CAB 3.5 mg	Yes	No
5	61	0.6	0.5	377	1.82	186	0.90	318	1.54	OCT 30 mg	No	No
6	79	1.1	1.6	474	2.76	299	1.74	346	1.67	OCT 30 mg + CAB 3.5 mg	No	No
7	62	0.4	0.9	297	1.43	145	0.70	245	1.18	OCT 30 mg + CAB 3.5 mg	No	No
8	43	0.4	0.7	340	1.39	179	0.69	458	2.21	OCT 30 mg + CAB 3.5 mg	Yes	No
9	63	0.4	0.4	337	1.63	209	1.01	293	1.42	CAB 3.5 mg	Yes	No
10	57	1.7	0.6	594	2.70	188	0.85	407	1.97	OCT 30 mg + CAB 3.5 mg	Yes	Yes
11	36	0.8	11.5	432	1.09	327	0.82	467	2.26	OCT 30 mg	Yes	No
12	42	0.7	0.9	384	1.47	207	0.79	406	1.96	CAB 3.5 mg	No	No
13	41	1.2	0.7	573	2.20	290	1.05	422	2.04	CAB 3.5 mg	Yes	Yes
14	73	0.4	0.5	279	1.52	232	1.26	283	1.37	CAB 3.5 mg	No	No
15	44	0.2	0.4	310	1.19	126	0.48			OCT 30 mg + CAB 3.5 mg	Yes	Yes
16	52	0.9	1.8	351	1.51	260	1.12	338	1.63	OCT 30 mg	Yes	No
Mean	52.8	0.9	1.6	424.2	1.8	250.1	1.1	391.1	1.9			
SD	12.6	0.6	2.6	108.2	0.5	83	0.4	94.2	0.5			

Abbreviations: Pre, baseline; Post, at the end of 3 months CC treatment; 3m P/WD, 3 months post withdrawal of CC; OCT, Oct-LAR.

were tested in a small number of patients. SERMs (tamoxifen and raloxifene) also demonstrated a potential use in some cases (4). Clomiphene citrate (CC) is a SERM that possesses positive estrogenic effect on the periphery and a negative effect at the hypothalamus and pituitary levels, thus increasing LH and FSH secretion and improving hypogonadism and fertility outcomes (5, 6).

The aim of this study was to assess the impact of CC treatment in male acromegaly patients, especially those with low T levels.

Patients and Methods

Patients

This study aimed to include patients with noncontrolled acromegaly despite the use of all available options in our center, which included pituitary surgery and radiotherapy, octreotide LAR (Oct-LAR), and cabergoline (CAB).

Sixteen male patients (median age, 52.5 y; range, 36–79 y) who were regularly followed at our neuroendocrine outpatient clinic were screened for entering the protocol. The inclusion criteria were: age between 18 and 80 years; patients with active acromegaly on regular use of a stable dose of Oct-LAR and/or CAB for at least 1 year; IGF-1 above the reference range during the last year of follow-up; and T levels within or below the third inferior tertile of normality. Serum total T levels were assessed in 13 patients. Three cases were on T replacement therapy and refused hormone withdrawal. The criteria of selecting patients only below or in the lower range of normality was chosen based on the beneficial effects of CC on serum T in hypogonadotropic hypogonadism (6).

Exclusion criteria included: radiotherapy in the last 10 years; previous venous embolism (including family members); previous prostatic cancer or symptomatic benign hypertrophy; triglyceride levels above 400 mg/dL; renal failure defined by estimation of renal filtration below 30 mL/min; liver disease defined by hepatic enzymes three times above the upper normal limit; active oncological disease in the last 10 years; and previous cardiac or cerebrovascular disease.

As shown in Table 1, four patients were only on Oct-LAR, and another four were only on CAB. In these cases, association was not performed due to intolerance to one of the drugs. The doses used were the maximum doses allowed in our center: 30 mg every 28 days for Oct-LAR, and 0.5 mg/d for CAB (3.5 mg/wk).

Four patients were submitted to radiotherapy more than 10 years before the beginning of the study. IGF-1 was reassessed 3 months after the completion of the study to rule out any potential long-term effects of radiotherapy.

The local ethics committee approved the study protocol, and all participants gave written informed consent before entering the study.

Study design

This was a prospective, open-label, single-center trial. CC (50 mg/d orally) was prescribed for 3 months as an add-on therapy together with Oct- LAR and/or CAB.

Clinical evaluation was performed before and at the end of the intervention.

Patients were asked to grade each of their symptoms at baseline and after therapy as: 0, absent; 1, mild; 2, moderate; 3, severe but not incapacitating; or 4, severe and incapacitating. The symptoms scored were: headache, perspiration, arthralgia, paresthesia, and fatigue.

Hormonal assessment was performed before and at the end of the intervention and 3 months after CC withdrawal. This evaluation included: GH, IGF-1, total T, FSH, and LH. Prostate-specific antigen was also evaluated. In those patients using Oct-LAR, blood tests were collected on the same day and before the drug administration. In this study, the maximum dosage used was 30 mg every 28 days for Oct-LAR and 0.5 mg daily (3.5 mg/wk) for CAB. Because this study did not have a control group, IGF-1 levels were assessed again 3 months after CC discontinuation to confirm the return to baseline levels. During the period of intervention and CC withdrawal, no changes in the drugs previously used (Oct-LAR and/or CAB) were permitted.

Laboratory assays

Plasma GH and IGF-1 levels were assayed by immunoassays using commercially available kits. GH levels were determined by fluoroimmunoassay with monoclonal antibodies (AutoDELFIA; Wallac). Analytical sensitivity of this assay was better than 0.03 mU/L. Intra- and interassay variation was lower than 5.1%. The standards have been calibrated against the World Health Organization (WHO) First International Standard (80/505). IGF-1 was determined by solid-phase enzyme-labeled chemiluminescent immunometric assay (IMMULITE 2000 IGF-1; Siemens Healthcare Diagnostics). The standards have been calibrated against the WHO NIBSC First RR 87/518. Analytical sensitivity of this assay is better than 20 ng/mL. Intra- and interassay variation was lower than 8.1%. The manufacturer gave the references of normality used, and the IGF-1 values were expressed as absolute and/or as times above upper limit of the normal range (xULNR).

Statistical analysis

Measures of central tendency (mean) and variability (range and/or SD) were used to describe numeric variables. Paired Student's *t* test was used to verify the mean differences between dependent normally distributed variables. Wilcoxon sign test was performed to non-normally distributed dependent variables. A significance level of 5% was adopted for all statistical tests ($P < .05$). The statistical software STATA version 7.0 (StataCorp) was used to perform all statistical analyses. Values were expressed as mean ± SD.

Results

Patient characteristics and drugs in use during treatment are shown in Table 1.

After 3 months of the intervention, patients demonstrated a trend toward improvement of their signs and/or symptoms, as shown in Table 2.

At baseline, serum GH levels lower than 1 ng/mL were observed in 10 of 16 patients, whereas serum IGF-1 levels were elevated in all patients. At the end of the study, serum IGF-1 levels decreased by 41% (424 ± 108 to 250 ± 83 ng/mL; $P < .0004$) (Figure 1), leading 44% (seven of 16) of patients to achieve normal IGF-1 levels (Figure 2). Patients were considered controlled when IGF-1 levels, at the end of the treatment, were normal (below 1.00 xULNR). Regarding GH levels, despite the elevation observed in a single patient during CC treatment, the mean GH levels did not show a significant change (0.90 ± 0.6 to 1.6 ± 2.6 ng/mL; $P = .36$). Three months after CC withdrawal, GH and IGF-1 levels were reassessed in 15 patients; only patient 15 was lost to follow-up. The mean serum IGF-1 value rose to 391 ± 94 ng/mL with a $P < .0006$, and the mean serum GH level decreased to 0.86 ± 0.4 ng/mL, a value similar to baseline levels ($P = .28$).

In the 10 patients assessed, mean total serum T levels increased by 209% (282 ± 210 to 497 ± 310 ng/dL; $P = .02$), reaching normal levels in 67% (four of six) of those patients considered hypogonadal. In the two patients who did not achieve normalization, T levels remained unchanged after the trial with CC (Table 1). Serum FSH and LH levels rose (6.9 ± 10.0 to 8.6 ± 13.0 IU/L, $P = .15$; and 3.4 ± 3.0 to 5.2 ± 6.0 IU/L, $P = .22$, respectively), however, not reaching significant differences. Despite the increase of T, serum prostate-specific antigen remained stable (mean, 2.0 ± 2.0 to 2.2 ± 2.0 ng/mL; $P = .91$).

Discussion

Despite advances in acromegaly treatment achieved by surgery, radiotherapy, and medical therapy, a subgroup of

Table 2. Signs and Symptoms Before and 90 Days After Treatment With CC

	Headache		Perspiration		Arthralgia		Paresthesia		Fatigue	
Patient No.	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	0	0	0	0	0	0	0	0	0	0
2	1	1	1	1	2	2	0	0	3	3
3	2	1	0	0	1	0	1	0	1	1
4	0	0	1	0	1	0	0	0	0	0
5	1	0	0	0	2	2	0	0	1	1
6	0	0	1	1	2	2	1	1	1	1
7	0	0	1	0	1	0	1	0	2	0
8	1	0	1	1	0	2	0	0	4	2
9	2	1	0	0	3	1	1	0	2	0
10	0	0	0	0	2	1	1	1	2	1
11	1	0	2	2	3	2	1	1	3	2
12	1	0	0	0	0	0	0	0	2	1
13	2	0	1	0	2	1	2	0	1	0
14	1	0	0	0	2	0	0	0	0	0
15	NA	0	NA	0	NA	0	NA	0	NA	0
16	0	0	0	0	0	0	0	0	0	0
Sum	12	3	8	5	21	13	8	3	5	5

Abbreviation: NA, not available. Grade of each of the signs and symptoms: 0 = absent; 1 = mild; 2 = moderate; 3 = severe but not incapacitating; or 4 = severe and incapacitating.

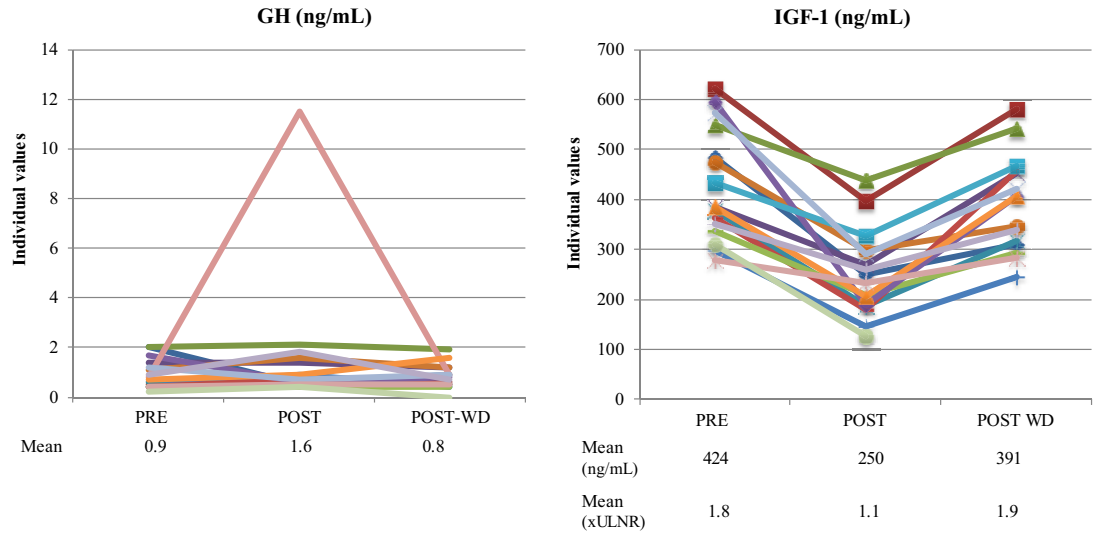

Figure 1. Individual GH (left) and IGF-1 (right) levels of 16 acromegalic patients. At the end of CC (POST), GH levels showed a nonsignificant increase ($P = .36$) and IGF-1 levels were reduced by 41% ($P < .00004$). After CC withdrawal (POST-WD), GH and IGF-1 levels returned to baseline.

patients still remains uncontrolled. For those patients, the next pharmacological option would be the GH receptor antagonist (pegvisomant) (7). However, the high cost and the lack of availability limit its prescription in many centers around the world.

In the past, estrogens were used to treat acromegaly, accomplishing almost a 50% decline of IGF-1 values, but as a result of side effects caused by the high doses administered, this class of drugs was discontinued, especially after new medications became available (2, 8, 9).

SERMs are molecules derived from estrogen that harbor an agonist effect on some organs and an antagonist effect on others.

The first SERM tried for acromegaly treatment was tamoxifen. This drug is frequently used for women with breast cancer due to its antagonist action on estrogen receptors on breast cells. Cozzi et al (10) assessed the effect of tamoxifen in 19 acromegalic patients (six males and 13 females) and obtained a significant reduction of IGF-1 levels (29.6%), reaching hormonal control in 21% of

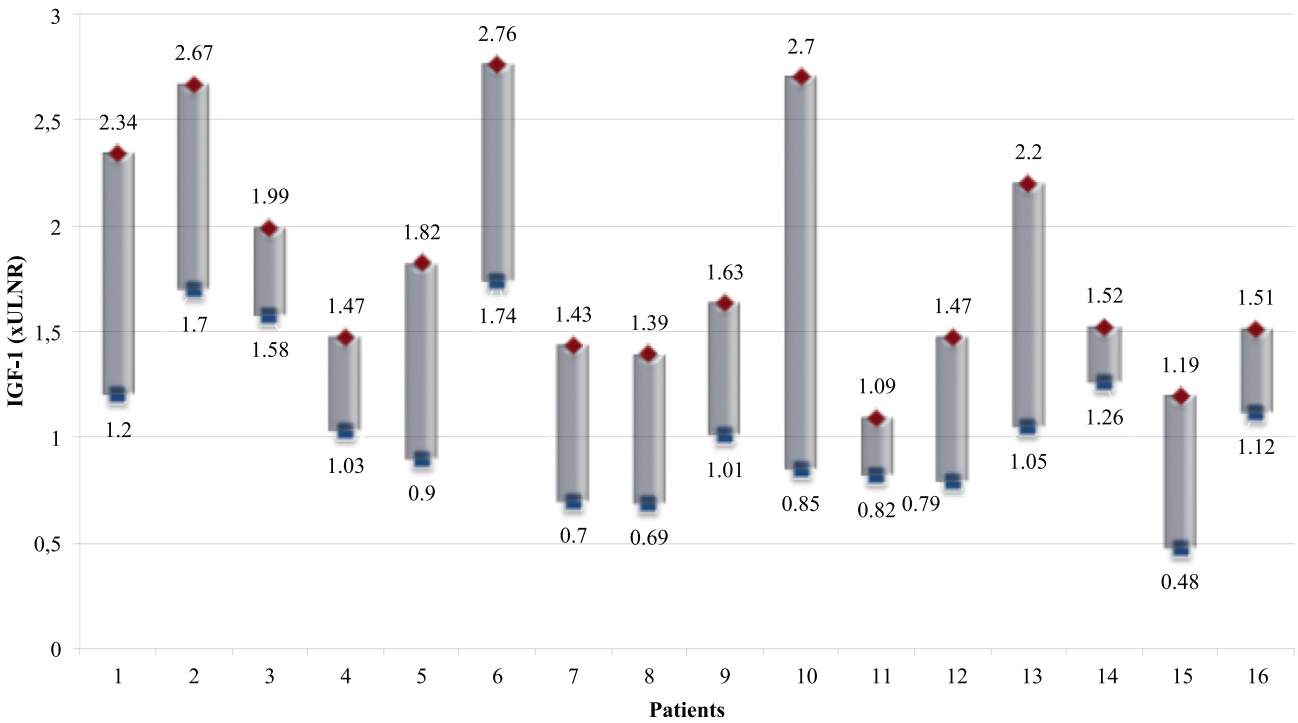

Figure 2. IGF-1 levels before (top) and at the end (bottom) of CC treatment.

cases in both genders. Interestingly enough, a case report showed an important IGF-1 decline attaining hormonal control with tamoxifen use in a patient with an IGF-1 value 4.1 xULNR at the beginning of the treatment (11). Recently, Balili and Barkan (12) conducted another study with tamoxifen for 4 months in 17 patients with biochemically active acromegaly (15 men and two postmenopausal women) and realized a decrease of circulating IGF-1 in 14 patients (82%) and hormonal normalization in eight (47%). No increase in GH levels was observed (12).

A few years after the first tamoxifen trial, Attanasio et al (13) tested another SERM, raloxifene, on postmenopausal acromegalic women and observed a 35% reduction of IGF-1 levels, reaching hormonal control in 54% of the cases. Dimaraki et al (14) used the same SERM for nine men and observed a mild reduction of 16% in IGF-1 levels, achieving "safe" hormonal levels in only 25% of patients.

Most recently, Vallette and Serri (3) added a combination of estrogen and progesterone (20 μg ethinyl estradiol and 100 μg levonorgestrel) to 11 women uncontrolled by surgery (seven patients were receiving Oct-LAR, and four were off medications) and obtained hormonal control in 73% of their cases.

A recent meta-analysis demonstrated that women receiving estrogen had a significant IGF-1 reduction, greater than that observed with the use of SERMs. In acromegalic male patients treated with SERMs, only a trend in IGF-1 reduction was observed. However, this study concluded that estrogen and SERMs could be used to achieve hormonal control when the disease is refractory to current treatment (4).

Initially, the proposed mechanism of estrogen action to cause reduction of IGF-1 levels was a reduction of the expression of GH receptors on the cells (15). Later, Leung et al (16) demonstrated that estrogen up-regulates the expression of suppressors of cytokine signaling-2 (SOCS2) in a dose-dependent way. This protein impairs GH-induced Janus kinase 2 phosphorylation attenuating intracellular GH signaling and, by consequence, reduces IGF-1 production (17, 18). Estrogens can also suppress GH receptor signaling throughout nongenomic pathways by inducing phospholipase C activation that could lead to nuclear translocation of signal transducers and activators of transcription (STAT) 3 and STAT5 and cause desensitization of Janus kinase/STAT signaling due to reduced availability of STAT proteins in the cytoplasm (19).

The route of estrogen administration is crucial for this effect. Oral administration of estrogen caused a 3-fold decrease in IGF-1 levels in postmenopausal women, whereas transdermal estrogen only induced a small increase (20). The first-pass mechanism with liver exposition to higher levels of estrogen is supposed to explain the different actions between oral and transdermal routes.

Serum GH levels can be augmented during oral estrogen treatment. The supposed mechanisms are an increase in GH binding protein levels (21) and reduced IGF-1 feedback (20). Such elevation was not observed in the present study.

CC is a SERM with estrogenic and antiestrogenic properties, depending on the organ. In the hypothalamic-pituitary axis, CC exerts antiestrogenic effects competing with estrogen for their receptors. The activation of those receptors by CC blocks the estrogen feedback, leading to an increase of LH and FSH secretion by the pituitary. On the periphery, CC has a weak estrogenic activity. Due to these characteristics, CC is frequently used for fertility treatment. However, this therapy would be ineffective in patients with severe compromise of the gonadotropic axis.

The reduction of IGF-1 levels under CC treatment was previously described in normal women, in patients with polycystic ovarian syndrome, or in fertilization treatment (22–24), with reductions ranging from 22 to 35%.

Ribeiro and Abucham (25) demonstrated that CC was able to restore normal T levels and to improve sperm motility in male patients with prolactinomas and persistent hypogonadism under DA therapy. The recovery of gonadal function by CC was independent of prolactin. In our study, four of six patients achieved normal T levels after CC treatment. Conversely, possible severe damage of the gonadotropic axis occurred in two patients of our cohort, preventing restoration of androgenic levels.

Because the GH receptor antagonist is not available in many countries, there is a need for other options when surgery, drugs (SRLs and/or DA), and radiotherapy fail to achieve acromegaly control. CC could be an option for men, especially for those with low or normal/low T levels. For those men with normal/high levels of T, CC should be cautiously prescribed because this cohort may achieve hormone levels above the normal range leading to adverse effects. Although the scope of this study did not include women, CC could potentially be used for postmenopausal patients, but it should be avoided in women of reproductive age due to the risk of ovarian hyperstimulation syndrome.

Our data suggest that CC acts in the liver, reducing the pool of circulating IGF-1 similar to estrogens. However, its action on peripheral tissues is still a matter of debate.

Recently, Bolamperti et al (26) showed an opposite effect of estrogens on IGF-1 modulation in human osteoblasts. In these cells, addition of estrogens reduced dose-dependently SOCS2 protein levels, amplifying GH intracellular signaling. Further studies are needed to clarify the effect of estrogens and SERMs (including CC) on peripheral sites, which could be tissue dependent.

The concern about peripheral action of GH and IGF-1

should always be kept in mind when treating acromegalic patients. Neggers et al (27) raised the issue of extrahepatic acromegaly, showing that different levels of GH could result in different peripheral outcomes even with the same level of IGF-1. This condition points to the use of other tools for monitoring patients during treatment, as quality of life questionnaires and the accurate assessment of clinical changes. During our study, patients demonstrated a trend toward improving their symptoms of acromegaly (Table 2), in line with serum IGF-1 reduction.

In the present study, 10 of 16 patients (62%) showed apparent discordant GH and IGF-1 levels (elevated IGF-1 and normal GH). GH/IGF-1 discordancy has been reported in up to 39% of acromegalic patients being treated with SRLs and other therapies (28–30). Mechanisms for this dissociation (normal GH and high IGF-1 levels) are still a matter of debate, but among the alleged mechanisms we can include: GH receptor polymorphism (31), abnormal GH pulsatility (32), and previous radiotherapy (33, 34). Nevertheless, the apparent discordancy could simply be due to the low serum GH values as a function of the commercial assay used in our study. Another possible confounding factor is the use of IGF-1 assays not calibrated with the current standard 02/254, which could lead to different approaches during follow-up (35).

A normalized serum IGF-1 level is an accepted definition of disease control (36) and has been proven to be a reliable predictor of mortality in acromegaly (37, 38). Alexopoulou et al (28) evaluated noncured acromegalic patients of the Belgian acromegaly registry (AcroBel). They found that patients with high IGF-1 but normal GH, although without differences in clinical symptoms of acromegaly, showed a worse metabolic profile compared with patients with high GH and normal IGF-1. They also showed that IGF-1, but not GH, was a strong independent predictor of diabetes mellitus. Their data suggest that high IGF-1, rather than high GH, is indicative of persistently active disease. Interestingly enough, the group of normal GH and high IGF-1 levels had a preponderance of male acromegalic patients.

No side effects were reported during treatment, and the main concern was to advise the patients regarding situations that could increase the chance of thrombosis once CC could have some degree of influence on coagulation, in the same way that oral estrogens and other SERMs have.

Further studies are necessary to assess the safety of long-term treatment and, in those that did not achieve hormonal control, to access the efficacy of dose increase. Another point to be considered, in line with data of the GH receptor antagonist, is the concern of tumor growth due to the reduction of IGF-1 feedback, especially in those patients that did not receive radiotherapy. In our study, despite no significant change of mean serum GH levels, one patient exhibited an increment in his GH level that returned to baseline after CC withdrawal (Figure 1). In the case of longstanding treatment, assessment of tumor volume by magnetic resonance imaging should be performed at 6 and 12 months after treatment initiation, and if there is no size change at 1 year, it should be done yearly, according to The Endocrine Society guidelines on acromegaly (39).

Conclusion

The results we obtained open a new perspective for male patients not controlled after surgery and SRLs. Additionally, improvement of T was obtained in those patients that apparently had some degree of gonadotropic reserve.

Our results show that the addition of CC should be considered as an option in male acromegaly patients not controlled by current available options, with a considerable cost-saving system. In Brazil, CC 50 mg costs about US $40 (per month), in contrast to the estimated cost of US $6000 (per month) for pegvisomant, the next choice in the treatment algorithm (40).

Furthermore, improvement of T levels can be obtained in those patients with concurrent central hypogonadism.

Finally, we suggest that estrogen and SERMs should be included in the next guidelines for acromegaly treatment as an option for those patients who do not attain hormonal control with current drugs, an opinion that is shared by other investigators (4, 41).

Acknowledgments

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Disclosure Summary: M.D.B. is a consultant and a member of steering committees at Ipsen and Novartis; a speaker for Ipsen, Novartis, and Pfizer; and principal investigator of clinical trials for Novartis. F.H.D. and R.S.J. have nothing to declare.

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