Abstract

Background: IGF-I suppression in acromegaly obtained by tamoxifen, a selective estrogen receptor modulator (SERM), prompted us to evaluate the effects of the administration of a newer SERM, raloxifene (RAL), devoid of estrogenic activity at uterine level, on GH/IGF-I levels in patients with this disease.

Patients: Thirteen post-menopausal acromegalic women (aged 55–84 years) with active acromegaly entered a prospective open pilot study of RAL treatment at 60 mg/day. Nine of the patients, who were resistant to somatostatin analog and dopamine agonist treatment, were not undertaking therapy; the other four, who were partially sensitive to medical treatment, maintained treatment at the maximally effective dosages throughout the study.

Results: IGF-I levels fell significantly from 444 (median, interquartile 393–590) μg/l to 300 (216–608) μg/l (P = 0.0192) after 1 month of RAL administration and this fall remained stable up to the final evaluation at 5±1 months from the start of RAL treatment (260 (187–410) μg/l). An IGF-I decrease greater than 30% of basal values was observed in 10 patients (mainly in patients with IGF-I levels lower than 600 μg/l) and normal values were reached in seven (54%). GH levels did not change (basal 6 (4.1–8) μg/l, final 5.5 (3.2–7.4) μg/l). The clinical picture improved in patients sensitive to RAL. RAL withdrawal was followed by the return of IGF-I levels to pretreatment values within 8 weeks in all patients.

Conclusions: RAL decreases IGF-I levels in most acromegalic women with mild or intermediate disease (i.e. with values lower than 600 μg/l) and normalizes it in many. A prospective randomized study in patients resistant or partially sensitive to other medical treatments is warranted.

Introduction

Acromegaly is an insidious chronic disease caused by unrestrained hypersecretion of GH, usually by a pituitary adenoma, that leads to increased mortality due tocardiological and oncological diseases. Treatment is usually neurosurgery (1). In patients unsuitable or unwilling to undergo neurosurgery, after its failure, or in selected cases as primary treatment (2), medications have been employed to reduce GH/IGF-I hypersecretion. Long-acting dopamine agonists (DA), such as cabergoline (3, 4), and somatostatin analogs (SA), such as lanreotide-SR (5) and octreotide-LAR (6), have been consistently shown to reduce hormonal hypersecretion in most patients and to normalize it in many. Epidemiological studies have shown the restoration of increased mortality associated with active acromegaly to values superimposable on those of a control population after achieving ‘safe’ GH levels (i.e. < 2.5 μg/l), regardless of the therapeutic modality (7, 8). However, SA and/or DA, given at the maximally effective or tolerated doses, do not normalize GH/IGF-I values in more than 30% of acromegalic patients (1).

Old literature data showing somatomedin-C suppression in patients with acromegaly by oral estrogen (E) use (9), and more recent data showing IGF-I suppression in acromegalic patients assuming selective estrogen receptor modulators (SERM), such as tamoxifen (TAM) (10), prompted us to evaluate the effects of raloxifene (RAL) in acromegalic women. RAL is a SERM with anti-estrogenic properties: it partially mimics the effects of estrogen in bone and the cardiovascular system, while it functions as an anti-estrogen in endometrial and breast tissue (11). It would work as an anti-estrogen on estrogen alpha-receptors and as estrogen on estrogen beta-receptors (12).

Patients and methods

Patients

Thirteen post-menopausal acromegalic women (aged 55–84 years) with active acromegaly according to clinical picture, GH levels not suppressible below 1 μg/l by oral glucose load and high age-matched IGF-I levels, entered a prospective open pilot study. All had high FSH and low estradiol levels. The patients’ individual demographic and clinical data are detailed in Table 1. Eight of them had been treated by neurosurgery at least 1 year before the study (in six, nos 4, 7,
Table 1 Demographic and clinical data of patients with active acromegaly.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Tx1</th>
<th>RxT2</th>
<th>CT/MR3</th>
<th>Hypopit4</th>
<th>AntiGH5</th>
<th>GH6</th>
<th>IGF-I6</th>
<th>Duration7</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>–</td>
<td>+</td>
<td>ES</td>
<td>–</td>
<td>off</td>
<td>20</td>
<td>1000</td>
<td>1</td>
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<tr>
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<td>69</td>
<td>–</td>
<td>–</td>
<td>ES</td>
<td>T</td>
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<td>4.2</td>
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<td>4</td>
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<tr>
<td>3</td>
<td>68</td>
<td>–</td>
<td>–</td>
<td>M</td>
<td>–</td>
<td>off</td>
<td>8</td>
<td>800</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>+</td>
<td>–</td>
<td>R</td>
<td>TA</td>
<td>CAB</td>
<td>4.1</td>
<td>476</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>–</td>
<td>–</td>
<td>M</td>
<td>–</td>
<td>LAR</td>
<td>11.4</td>
<td>444</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>84</td>
<td>–</td>
<td>+</td>
<td>M</td>
<td>–</td>
<td>off</td>
<td>1.9</td>
<td>353</td>
<td>2</td>
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<td>7</td>
<td>55</td>
<td>+</td>
<td>+</td>
<td>R</td>
<td>T</td>
<td>off</td>
<td>3.7</td>
<td>455</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>55</td>
<td>–</td>
<td>–</td>
<td>M</td>
<td>–</td>
<td>LAR</td>
<td>7</td>
<td>680</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>65</td>
<td>+</td>
<td>–</td>
<td>R</td>
<td>–</td>
<td>off</td>
<td>4</td>
<td>330</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>55</td>
<td>+</td>
<td>+</td>
<td>R</td>
<td>T</td>
<td>LAR</td>
<td>7.9</td>
<td>403</td>
<td>4</td>
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<tr>
<td>11</td>
<td>72</td>
<td>–</td>
<td>–</td>
<td>ES</td>
<td>A</td>
<td>off</td>
<td>8</td>
<td>590</td>
<td>6</td>
</tr>
<tr>
<td>12</td>
<td>72</td>
<td>+</td>
<td>+</td>
<td>R</td>
<td>T</td>
<td>off</td>
<td>6</td>
<td>430</td>
<td>6</td>
</tr>
<tr>
<td>13</td>
<td>62</td>
<td>+</td>
<td>+</td>
<td>R</td>
<td>–</td>
<td>off</td>
<td>5.5</td>
<td>390</td>
<td>6</td>
</tr>
</tbody>
</table>

1Neurosurgery; 2Radiotherapy; 3Neuroradiological imaging: M, macroadenoma; ES, empty sella; R, post-surgical remnant; 4Pituitary failure; T, thyroid; A, adrenal; 5GH-suppressive treatment; CAB, cabergoline; LAR, octreotide-LAR; 6Basal values in μg/l; 7Treatment duration in months.

9, 10, 12, 13) and/or radiotherapy at least 5 years before (in six, nos 1, 6, 7, 10, 11, 12). None of the patients were hyperprolactinemic. At neuroradiological pituitary imaging four had macroadenoma, six had remnants of pituitary adenoma invading the cavernous sinus, and three had empty sella.

Nine patients (nos 1–3, 6, 7, 9, 11–13), who were resistant to depot SA and DA treatment (i.e. GH decrease less than 30% as compared with baseline after at least three months of treatment at full dosages), were evaluated off medical treatment, from which they had withdrawn at least 6 months before the study. The other four were partially sensitive to medical treatment, i.e. they had persistently pathological IGF-I levels during chronic depot SA or DA treatment. They were evaluated while receiving treatment with long-acting SA (in three, nos 5, 8, 10), or DA (in one, no. 4) at the maximally effective dosages, as shown by the lack of any significant hormonal change between the last two evaluations.

Substitution treatment with L-thyroxine or cortisone acetate was administered regularly as required, in five (nos 2, 4, 7, 10, 12) and two patients (nos 4 and 11), respectively, at dosages kept constant throughout the study period. No patients had taken sex steroids for at least 6 months prior to the study.

Each patient gave informed consent after full explanation of the purpose of the study, which was approved by the Ethic Committee of our hospital. Procedures followed were in accordance with the Helsinki Declaration of 1975 and following revisions.

**Procedures**

RAL was given at the dosage of 60 mg/day. A careful clinical evaluation detailing frequency of headaches, swelling and ring size was checked on an outpatient basis. Blood analyses and clinical scores were assessed 3 months before RAL treatment began (T−3), immediately before the beginning of treatment (T0), and at monthly intervals thereafter. Hormonal and clinical assessments were repeated 2 months after RAL withdrawal. In patients on depot SA treatment, control assessments were performed on the same day as the administration of the drug before the therapy was given. After an overnight fast and rest, blood samples were collected in the morning hourly for 3 h while the patients were supine and awake, with an indwelling needle inserted in an antecubital vein and kept patent by slow infusion of saline. GH concentrations were assayed on each sample (values reported as the mean of the three samples in Results section), and IGF-I concentrations on the first sample only.

**Methods**

To avoid interassay variations, samples collected at T0 and after 1 month of RAL treatment (T1) were run in the same assay. GH (DPC, Los Angeles, California, USA) and IGF-I (Nichols, San Juan de Capistrano, California, USA) were assayed in duplicate by immunometry and RIA after acid–ethanol extraction, respectively. The GH detection limit was 0.01 μg/l. Standards were calibrated against first international reference preparation (IRP) 80/505 (1 ng = 2.6 μIU) for GH, and WHO 87/518 for IGF-I. Intra- and interassay coefficients of variation were 2.9–4.6 and 4.2–6.6% for GH, and 3.7 and 7.2% for IGF-I. In our laboratory, normal values for IGF-I are 71–290 μg/l in patients older than 55 years.

Serum total and HDL cholesterol, triglycerides, glucose, glycated hemoglobin A1c (HbA1c), insulin and C-peptide, as well as safety laboratory parameters, were assayed with standard methods both before and at the end of the study period.

**Statistical analysis**

IGF-I values are expressed both as absolute values and as a percentage of the upper limit of the normal age-matched range (%ULNR). Analyses were performed by GB-Stat 6.5.4 PPC (Dynamic Microsystems Inc., Silver Spring, Maryland, USA).
Spring, MD, USA) on raw data, or after transformation of hormonal data in percentage of the baseline.

Data were analyzed by non-parametric tests because they did not pass the preliminary Kolgomorov–Smirnov test for normality. Thus, values are expressed as median and interquartile ranges (25–75%), unless otherwise stated. Continuous data were analyzed by Wilcoxon test, Mann–Whitney U test, Kruskall–Wallis test followed by Dunn test, and Spearman correlation test. Categorical data were analyzed by Fisher’s exact test. All statistical tests were two-tailed and values of $P$ less than 0.05 were considered significant.

**Results**

Treatment was prolonged for a mean of 5.2 months ($\pm 0.8$ s.e.m.) (median 6, range 1–12). GH/IGF-I levels at T−3 and T0 were superimposable. IGF-I levels declined from 444 (median, interquartile 390–590) $\mu$g/l at T0 to 300 (216–608) $\mu$g/l at T1 ($P = 0.0192$), and this fall remained stable up to the last evaluation (260 (187–410) $\mu$g/l). The values expressed as ULNR were 153 (134–203), 95 (63–148), and 90 (64–141)%, respectively (Figs 1 and 2).

The median percent decrease was 35% (29–47%), as compared with baseline values. The decrease was greater than 30% in 10 patients. IGF-I reached age-matched normal values in seven of these (nos 2, 6, 7, 9, 10, 12, 13). In the remaining three patients, RAL was poorly effective: IGF-I levels did not change in patient no. 3 and increased in patient no. 8 (no. 1 dropped out after the first month of treatment).

At the retrospective evaluation of results, all patients whose basal IGF-I levels were lower than 600 $\mu$g/l achieved hormonal decrease or normalization. On the contrary, GH levels did not change during treatment (basal 6 (4.1–8) $\mu$g/l, final 5.5 (3.2–7.4) $\mu$g/l, $P = NS$). Basal GH levels were not different in patients sensitive to RAL treatment as compared with patients in whom this treatment was ineffective. IGF-I decline was observed both in patients on concomitant GH-suppressive treatment and in those off treatment. In all patients IGF-I returned to pretreatment levels after withdrawal from treatment (data not shown).

Most patients sensitive to treatment reported an improvement of clinical symptoms of the disease, i.e. swelling decreased in five out of eight patients, headache was ameliorated in three out of five, and an objective decrease in ring size was observed in six out of 11.

No significant change was observed in serum levels of glucose, HbA1c, cholesterol, triglycerides, insulin, C-peptide or safety parameters in the whole group (data not shown). In two diabetic patients, (nos 9 and 10), insulin requirement was lessened during RAL treatment.

**Discussion**

RAL administration was indeed effective in decreasing IGF-I levels in most acromegalic women, until its normalization in 54% of the series, without significant GH changes. This effect was not dependent on concomitant medical treatment aiming at inhibition of GH levels. IGF-I suppression was observed mainly in patients with basal IGF-I levels less than 600 $\mu$g/l, whereas in patients with higher levels of IGF-I, suppression was not achieved or was less evident, regardless of basal GH levels. As for the clinical picture, all patients sensitive to RAL treatment reported an improvement of symptoms linked to disease. Even though mean HbA1c and C-peptide did not change, a better metabolic control was observed in two diabetic patients.

RAL treatment obtained similar results on IGF-I values in post-menopausal women, both in osteoporosis (13) and in breast cancer (14). IGF-I suppression obtained by RAL both in the present study and in other diseases seems to correspond with results obtained in previous studies by another SERM, TAM. Administration of TAM for 2 months was indeed successful in reducing IGF-I levels in 13 out of 19 acromegalic patients (until normalization in four of them), without concomitant GH changes (10).
Moreover, TAM was reported to decrease IGF-I levels both in late puberty (15) and post-menopausal breast cancer (16). No change in IGF-binding proteins (BPs) was observed with the use of either drug.

The mechanism underlying IGF-I suppression after SERM treatment is far from clear. Even though expression of alpha-, beta- and splice variant isoforms of estrogen receptors has been shown in different proportions in the different types of pituitary tumors (17, 18), the lack of change in GH levels in our series rules out a central action at the pituitary or hypothalamic level.

A peripheral mechanism of action at the hepatic level and in the other organs where IGF-I is synthesized is therefore plausible. Experimental data have indeed shown that TAM suppresses liver IGF-I gene expression (19) and that IGF-I promoter on the hepatocyte cell line Hep3B is transcriptionally regulated by RAL after transfection with estrogen alpha-receptor (20).

In virtually all clinical studies, oral administration of estrogen reduced plasma IGF-I concentrations by 15–35% (reviewed in 21). The direct comparison always showed that only the oral administration of estrogen induces IGF-I suppression, whereas the transdermal application causes either no IGF-I change (22–26), or an increase in IGF-I (27). Our result suggests that RAL, notwithstanding its anti-estrogenic properties at the endometrial and the breast level, exerts a pure estrogenic action both at the hepatic and the peripheral level. These results have also been recorded with TAM. The lack of changes in GH levels in this study is unclear: GH did not change in patients assuming standard GH-suppressive treatments, or those off treatment too.

Estrogen is a prominent stimulus to GH secretion throughout the human life span, albeit via neuroendocrine mechanisms that are incompletely defined (28). Nearly all studies showed that oral estrogen, but not transdermal estrogen, increases basal GH levels in post-menopausal women (22, 23, 27–34). This effect does not seem to be dependent on IGF-I changes (21). Moreover, it was reported that GH suppression induced by oral glucose load is more pronounced in males than in females (35).

Conversely, contrasting data have been reported for TAM. A direct stimulatory effect on human adenomatous GH-secreting cells exposed in vitro to TAM was shown by Giustina et al. (36). TAM was reported to suppress GH secretion in rats with a mechanism mediated at least in part by stimulation of endogenous somatostatin (37). The observed lack of GH changes in our patients might therefore be accounted for by the autonomous GH secretion in acromegaly. This would not be sensitive to IGF-I feed-back, whereas the endogenous somatostatin secretion would be already maximally stimulated and thus not capable of further increase (38).

Epidemiological data have confidently shown the reduction to normality of the relative risk of cardiovascular and oncological death in acromegalic patients after the decrease of GH with any treatment to ‘safe’ levels (7, 8). Data trending in the same direction are also emerging for the restoration of age-matched IGF-I levels (39), but there are no data concerning the long-term outcome in patients whose IGF-I values normalized in spite of unchanged or increased GH levels.

In spite of the clinical improvement observed in the patients responsive to RAL administration, the decline in IGF-I levels without a corresponding GH change might be regarded only as a biochemical variation, because it has been recently hypothesized that the plasma compartment of IGF-I, deriving mainly from liver, might work only at restraining circulating GH levels (40). The peripheral compartment (at the level of bone, muscle, etc.) would thus have a minor influence on circulating IGF-I levels, but might still play the chief role on the pathophysiological scenario of the GH/IGF-I axis. This treatment might thus leave GH action on peripheral tissues unaffected. Of course a clinical study like ours cannot assess the relative contribution of the peripheral versus the hepatic component of circulating IGF-I. However, experimental data showed that estradiol down-regulates the expression of IGF-I and IGF-I receptor in peripheral cells (i.e. the smooth muscle vascular cells (41)). Also clinical data point out that estrogen can exert a role on IGF-I synthesis even at the peripheral level, since in women affected by GH deficiency the effects on bone of substitutive GH therapy were lessened by the concomitant oral estrogen treatment as compared with transdermal estrogen treatment (AM Colao et al. unpublished observations).

Another limitation of this study is that IGF-BPs were not assayed. However, no change in these proteins has been reported in most studies after the administration of oral estrogen or SERMs (22, 24, 26, 42, 43).

In conclusion, this study shows that RAL is effective in decreasing and/or normalizing IGF-I levels in acromegalic women. It might be considered as an adjuvant tool in the medical equipment for this disease in patients partially sensitive or resistant to SA/DA treatments. Further appraisal by a prospective randomized study is warranted, to evaluate the effects of progressively increasing RAL dosages, as well as its effects in male and younger female patients.

References

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Received 30 July 2002
Accepted 4 December 2002

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