Evaluation of IGF-I levels during long-term somatostatin analogs treatment in patients with gastroenteropancreatic endocrine tumors

C. L. Ronchi¹, M. Peracchi², S. Corbetta¹, S. Massironi², C. Ciafardini², D. Conte², P. Beck-Peccoz¹, and A. Spada¹
¹Unit of Endocrinology; ²Unit of Gastroenterology, Department of Medical Sciences, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, University of Milan, Milan, Italy

ABSTRACT. Previous experiments reported desensitization to SS action in rat anterior pituitary cells and cell lines. The aim of the study was to verify whether the lack of desensitization to SS analogs (SSa) observed in acromegalic patients was also present in subjects with normal hypothalamic-pituitary function. The effect of chronic treatment with octreotide long-acting release (o-LAR, 10-30 mg/28 days) on IGF-I levels was then evaluated in 23 patients with gastroenteropancreatic (GEP) endocrine tumors (8 gastrinomas, 6 carcinoids, and 9 functioning pancreatic tumors). Serum IGF-I, clinical symptoms, plasma chromogranin-A (CgA) and markers of hepatic synthesis were evaluated before and after a short-term period in all the patients (median 4.5 months), after a medium-term period in 12 (median 18 months) and after a long-term follow-up period in 9 of them (median 48 months). Mean IGF-I levels decreased from 17.3±7.0 to 12.8±6.2 nmol/l in the short-term (p<0.005) being reduced from baseline concentrations in 87% and under the normal range for age in 35% of patients. Afterwards, they always remained stable both in the medium- and long-term periods, still being low in 3/12 and 2/9 patients, respectively. No alterations in biochemical markers of liver function were found either before or during therapy. No correlation between IGF-I levels, CgA concentrations and/or clinical definitive outcome was observed. In conclusion, the study demonstrated that: a) similarly to that observed in acromegalic patients, chronic o-LAR treatment did not induce desensitization of pituitary SS receptors (SSR) in humans with intact hypothalamic-pituitary axis, and b) in patients with GEP endocrine tumors, GH/IGF-I inhibition did not contribute to SSa efficacy.


INTRODUCTION
SS exerts potent inhibitory effects on secretion processes in several neuroendocrine tissues by binding to specific subtypes of SS receptors (SSR) (1-3). In the ‘80s, different synthetic SS analogs (SSa) that bind prevalently to SSR subtypes 2 and 5, both highly expressed in GH- and TSH-secreting pituitary adenomas and many endocrine tumors of the gastroenteropancreatic (GEP) system (4-6), were developed and introduced into the management of these diseases (7, 8). Up to date, novel long-acting formulations, such as octreotide long-acting release (o-LAR) and lanreotide slow release (9-13), are currently used. Desensitization, the tendency of biological responses to wane over time despite the continuous presence of a stimulus, frequently occurs in endocrine systems. In particular, several hypothalamic hypophysiotropic hormones cause desensitization to their own action in pituitary target cells. Accordingly, continued exposure to SS induces agonist-dependent reduction of response within hours to days in normal and tumorous rat anterior pituitary and islet cells (2, 8, 9, 14, 15). In clinical practice, chronic administration of SSa induces a rapid improvement of clinical symptoms and hormonal secretion in the majority of patients with GEP endocrine tumors, quite often followed by a delayed “escape” from treatment within weeks to months (6, 8, 11-13, 16). The long time frame of this loss of sensitivity may suggest the outgrowth of tumor clones lacking SSR rather than, or together with, a SSR down-regulation

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Correspondence: C. L. Ronchi, MD, Unit of Endocrinology, Department of Medical Sciences, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Via F. Sforza 35, 20122 Milano, Italy.
E-mail: cristina.ronchi@unimi.it
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at the tumor level (6, 8). On the contrary, SSAs cause a persistent inhibition of GH/IGF-I hypersecretion in acromegalic patients, increasing doses over time being exceptionally required in these patients (8, 17, 18). Indeed, up to now only few data on the chronic effect of pharmacological doses of SSAs on GH/IGF-I axis in normal subjects have been available. In fact, the information mainly concerns early (2-12 weeks) effects of short- or long-acting SSAs on small numbers of healthy subjects or diabetic patients (19, 20) or patients affected by different kinds of non-GEP endocrine carcinomas (21-25).

These previous findings raise the question of whether the lack of desensitization in acromegalic patients may be related to the tumorous nature of somatotrophs expressing SSR or may represent a characteristic of the normal human somatotrophs. In this respect, it is worth noting that desensitization to the action of GHRH seems to occur in normal somatotrophs and not in tumoral cells (26).

The aim of the present study was to evaluate the effects of long-term treatment with α-LAR on IGF-I secretion in human subjects with intact hypothalamic-pituitary-somatotroph axis, i.e. patients with GEP endocrine tumors and preserved hepatic function. Furthermore, we evaluated the correlation between IGF-I levels and the outcome of the disease during treatment.

MATERIALS AND METHODS

Patients

We studied a total of 23 patients (12 men and 11 women, mean age: 54.4±12.1 (SD) yr, body mass index (BMI): 24±4.3 kg/m²) with biopsy-confirmed diagnosis of GEP endocrine tumors (6 well-differentiated tumors and 17 well-differentiated carcinomas). In particular, 8 patients had isolated gastrinomas, 6 mid-gut carcinoids, 9 pancreatic tumors with clinical syndrome due to release of biologically active peptides, including SS (no. =4), pancreatic polypeptide (no. =7), neurotensin (no. =2), calcitonin (no. =1), vasoactive intestinal peptide (no. =1) and PTH-related peptide (no. =1). A total of 17 patients were also affected by lymph nodal and/or liver metastasis. Sixteen patients previously underwent debulking treatments (surgery, radiotherapy, thermal ablation, and/or chemoembolization) and 3 previously underwent chemotherapy. In any case, at study entry all the patients had preserved hemachrome values and hematological markers of renal and hepatic function, thus excluding a possible negative effect of previous treatments on hepatic IGF-I synthesis ability.

Study protocol

The patients were selected on the basis of positive OctreoScan® imaging and were subsequently treated with α-LAR at the initial dose of 20 mg i.m. every 28 days, afterwards adjusted to 10 or 30 mg every 28 days.

Evaluation of circulating IGF-I concentrations was performed at baseline and after short-term period of α-LAR treatment in all 23 patients (median: 4.5 months, range: 3-6) and then after medium-term period in 12/23 (median: 18 months, range: 12-24) and long-term period in 9/12 patients (median: 48 months, range: 36-96).

The efficacy of therapy was evaluated by the periodical assessment of clinical symptoms through a questionnaire along with the measurement of a biochemical generic tumor marker such as chromogranin-A (CgA) and specific tumor markers (gastrin, S-HIAA, SS, pancreatic polypeptide, neurotensin, calcitonin, vasoactive intestinal peptide, and PTH-related peptide). The severity of symptoms, such as diarrhea and flushing, was scored on a 4-point scale (27). On the basis of symptomatic and overall hormonal response to treatment, all the patients were subdivided into different categories of responsiveness (12). They were defined as well or partially responsive to treatment (normalization or reduction of at least 50% of basal symptoms score and biochemical tumor marker levels), non-responsive to treatment (reduction of less than 50% or increase of less than 25% of basal symptoms score and biochemical tumor marker levels), progressive (increase of more than 25% of basal symptoms score and/or biochemical tumor marker levels), or relapsing (increase of at least 25% of basal symptoms score and/or biochemical tumor marker levels after initial significant response). Tumor mass was also periodically determined by abdominal ultrasonography, computed tomography (CT) scan and/or magnetic resonance imaging (MRI).

Hematological markers of liver function were also regularly assessed during the study to exclude the influence of protein synthesis deterioration on IGF-I production.

The local Ethics Committee (Fondazione di Ricerca e Cura a Carattere Scientifico Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Milan) approved the protocol and all the patients gave their informed written consent.

Methods

After an overnight fast, all serum samples for IGF-I measurement were separated at room temperature and stored at –20 C until assayed, while plasma samples for CgA assays were collected in tubes containing heparin, immediately separated by centrifugation at 4 C and stored at –80 C. Serum IGF-I levels were measured by a commercial radio-immuno assay (RIA) kit from Medignost (Tübingen, Germany) with separation of IGF-I from binding proteins obtained by acidification in IGF-II excess. The intra- and inter-assay coefficients of variation were 3.2 and 8.9%, respectively and IGF-II cross-reactivity less than 0.05%. The values were compared with an appropriate age-adjusted range, as previously reported (28). Plasma CgA levels were measured by an enzyme-linked immunosorbent assay purchased by Dako A/S (Glostrup, Denmark), as previously reported (29).

All hematological markers of liver function such as serum total proteins, albumin, pseudocholinesterase and prothrombin time values were measured by routine commercial assays.

Statistical analysis

All results are expressed as mean±SD unless otherwise expressed (figures). IGF-I levels were compared with their age-appropriate absolute values normal range and were expressed both as absolute values and as standard deviation score (SDS). All data were tested for normality by the Kolmogorov-Smirnoff test and, where necessary, they have been log-transformed to approach normality. Statistical analysis was then carried out by one-way analysis of variance (ANOVA) for repeated measures followed by Bonferroni’s post-hoc test. Correlation coefficients between different