Resistance to Somatostatin Analogs in Acromegaly

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Somatostatin analogs (SA) are widely used in acromegaly, either as first-line or adjuvant treatment after surgery. First-line treatment with these drugs is generally used in the patients with macroadenomas or in those with clinical conditions so severe as to prevent unsafe reactions during anesthesia. Generally, the response to SA takes into account both control of GH and IGF-I excess, with consequent improvement of clinical symptoms directly related to GH and IGF-I excess, and tumor shrinkage. This latter effect is more prominent in the patients treated first-line and bearing large macroadenomas, but it is also observed in patients with microadenomas, even with little clinical implication. Predictors of response are patients' gender, age, initial GH and IGF-I levels, and tumor mass, as well as adequate expression of somatostatin receptor types 2 and 5, those with the highest affinity for octreotide and lanreotide. Only sporadic cases of somatostatin receptor gene mutation or impaired signaling pathways have been described in GH-secreting tumors so far. The response to SA also depends on treatment duration and dosage of the drug used, so that a definition of resistance based on short-term treatments using low doses of long-acting SA is limited. Current data suggest that response to these drugs is better analyzed taking together biochemical and tumoral effects because only the absence of both responses might be considered as a poor response or resistance. This latter evidence seems to occur in 25% of treated patients after 12 months of currently available long-acting SA. (*Endocrine Reviews* 32: 247–271, 2011)

I. Introduction

Acromegaly is a rare but severe endocrine disease resulting from the increased release of GH, and consequently IGF-I, induced by a pituitary adenoma (1). As reported in the most recent guidelines for management of acromegaly (2), the therapeutic goals include mortality reduction, tumor shrinkage, and treatment of comorbidities, in association with improvement of signs and symptoms related to the disease. Moreover, reduction in tumor size is desirable in the patients with GH-secreting pituitary macroadenomas to avoid the impingement on vital structures (2). Comorbidities, including cardiovascular and respiratory disease, arterial hypertension, metabolic complications, and arthropathy, frequently induce a chronic disability and impair quality of life in acromegalic patients (3). Therefore, any treatment of acromegaly aims at reducing the mortality rate to the same level as the general population so that life expectancy in these patients is brought back to normal.

Current available treatments for acromegaly include neurosurgery, radiotherapy, and medical therapy with

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Abbreviations: ATG, Autogel; BMI, body mass index; D_2, dopamine receptor type 2; DA, dopamine agonist(s); LAR, long-acting repeatable; OGTT, oral glucose tolerance test; PK, pharmacokinetic; PLC, phospholipase C; PTP, phosphotyrosine phosphatase; SA, somatostatin analog(s); SR, slow release; SSTR, somatostatin receptor(s).

dopamine agonists (DA), somatostatin analogs (SA), and more recently, the GH-receptor antagonist pegvisomant.

The objective of this review is to discuss the phenomenon of resistance to SA, and therefore, data concerning surgery, radiotherapy, DA, and pegvisomant are beyond the scope of the study. SA can be administered as first-line therapy or as second-line therapy in patients undergoing unsuccessful surgery and are currently considered a cornerstone in the treatment of acromegaly. All currently available formulations of SA [sc octreotide, octreotide long-acting repeatable (LAR), lanreotide slow release (SR), or aqueous gel formulation autogel (ATG)] produce their antisecretive and antiproliferative effects by binding and activating somatostatin receptors (SSTR), and particularly sst_2 and sst_5 subtypes, which are the most common receptor subtypes expressed by GH-secreting pituitary tumors (4–7).

Control of acromegaly is obtained by restoring GH physiological pulsatility, normalizing IGF-I values to the normal range, and removing tumor mass. According to Giustina *et al.* (8), biochemical control of acromegaly is defined on the basis of GH as fasting and after glucose load, and on the basis of IGF-I levels if: 1) random GH is below 0.4 μg/liter or mean integrated 24-h GH is below 2.5 μg/liter or GH nadir after 75-g oral glucose tolerance test (OGTT) is below 1.0 μg/liter; and 2) IGF-I is in the normal range adjusted for age and gender. The GH (9–14) and IGF-I limits (14–17) are supported by epidemiological studies that have shown reduced life expectancy in patients with GH and IGF-I levels above these cutoffs. It should be noted that no data correlating nadir GH after OGTT with mortality are currently available. Moreover, the GH cutoff has been originated by using old GH RIAs, whereas newer GH-specific assays have demonstrated that GH values below 2.5 μg/liter are not associated with IGF-I levels in the normal range for age and gender (18, 19).

Response to SA therapy, in terms of biochemical control, has been investigated in many studies, indicating that approximately 70% of patients treated with SA achieved GH levels less than 2.5 μg/liter in the presence of normalized IGF-I values (2). The major drawbacks of this analysis are the short follow-up, because most data are reported after a median period of 12 months; the exclusion of the effects on tumor mass; the lack of standardization of dosage; and the use of various drug formulations, generally in combination and not as single agents.

As for the effects on tumor mass, the initial data based on administration of octreotide did not show a straight tumor-shrinking effect, whereas the slow-release formulations (LAR, SR, and ATG) have demonstrated significant effects on tumor mass. In fact, Bevan (20) reported that SA could induce some tumor shrinkage in 52% of patients when used as first-line therapy and in 21% of patients when administered as adjuvant treatment. The effects on tumor mass are, however, relevant for interpreting in a complete way the therapeutic efficacy of SA. It is known that SA display some effects in an indirect way by inhibition of angiogenesis or in a direct way by their antiproliferative effects on tumor cells, mediated by SSTR.

It is a fact that a definition of SA resistance that takes into consideration both the biochemical and the tumor effects of this class of drugs is relevant to optimize treatment of patients with acromegaly. On the basis of published reports, apparently one third of patients receiving SA treatment failed to obtain control of acromegaly, and among the patients who did not achieve control of acromegaly, a minority (<10%) was considered to be resistant to medical therapy. It should be stated, however, that criteria of defining resistance to SA are lacking, and results are only related to a 6- to 12-month treatment effect on GH and IGF-I levels.

The major objective of this review is to provide a critical analysis of the literature on the efficacy of SA in acromegaly in an effort to offer a potential definition of SA resistance based on recent data.

II. Molecular Mechanisms of Somatostatin Analog Action

A. Somatostatin receptor structure

Somatostatin is a small cyclic peptide that is widely expressed throughout the central nervous system and in the periphery (21). In the central nervous system, somatostatin acts as a neurotransmitter in both a stimulatory and inhibitory manner, whereas in the periphery somatostatin exerts predominantly inhibitory actions on secretion processes as well as in cell growth and differentiation (21, 22). Somatostatin is generated by a proteolytic processing of larger precursor molecules, called prepro-somatostatin and pro-somatostatin, which form two biologically active forms of somatostatin, denominated SS-14 and SS-28, consisting of 14 and 28 amino acids, respectively (21). Somatostatin mediates its biological functions via five membrane receptor subtypes (23–26).

The SSTR subtypes ($sst_{1\text{-}5}$) are encoded by genes localized on different chromosomes (23–26). However, two forms of the sst_2 receptor, sst_{2A} and sst_{2B}, are generated via alternative splicing; the two isoforms only differ in the length of the cytoplasmic tail of the recep-

TABLE 1. Human SSTR properties and signaling

	SST1	SST2	SST3	SST4	SST5
Properties					
Chromosome	14q13	17q24	22q13	20p11	16p13
No. of amino acids	391	369/356	418	388	364
Molecular weight	42.7	41.3	45.9	41.9	39.2
Transcript size	4.3	1.1	1.1	1.2	1.1
Glycosylation sites	3	4	2	1	3
Signaling					
Adenylyl cyclase activity	↓	↓	↓	↓	↓(↑)
PTP activity	↑	↑	↑	↑↓	↑
MAPK activity	↑	↑↓	↑↓	↑	↓
K^+ channels		↑	↑	↑	↑
Ca^{2+} channels	↓	↓			
Na/H exchangers	↓		↓	↓	
PLC activity	↑	↑	↑	↑	↑↓
Phospholipase A2 activity				↑	
Effect on hormone secretion					
GH	↓	↓		↓	↓
Insulin		↓			↓
Glucagon		↓			
ACTH		↓			↓
Ghrelin		↓			
Effect on cell growth					
Cell cycle arrest	↓	↑↓	↓	↓	↑↓
Apoptosis		↑	↑		
Pharmacological affinity profile					
SS-14	2.26	0.23	1.43	1.77	0.88
SS-28	1.85	0.31	1.3	ND	0.4
Octreotide	1140	0.56	34	7030	7
Lanreotide	2330	0.75	107	2100	5.2
Pasireotide	9.3	1	1.5	>100	0.16

Data are derived from Refs. 23–35. ND, Not determined.

tors (27). SSTR belong to the family of the seven transmembrane domain G protein-coupled receptors, characterized in their structure by the seven putative transmembrane regions, a conserved motif at the cytoplasmic face of the third transmembrane domain, and N-linked glycosylation sites in the N-terminal domain (28).

The SSTR subtypes can be placed into two subgroups, somatostatin-1 and -2. The somatostatin-1 receptor group includes sst_2, sst_3, and sst_5, whereas the somatostatin-2 group includes sst_1 and sst_4 receptors. This classification is based on structural features of the receptor subtypes, but it is also strongly supported by the pharmacological properties of the receptors (28). The five SSTR subtypes all bind SS-14 and SS-28 with high affinity but can be divided into two subclasses on their ability to bind structural octapeptide analogs of somatostatin. The sst_1 and sst_4 do not bind octapeptide SA, whereas sst_2, sst_3, and sst_5 receptors display a high, low, and moderate affinity, respectively, octreotide and lanreotide (28).

Table 1 summarizes the main features of SSTR.

B. Somatostatin receptor signaling

The five SSTR subtypes share a coupling to the second messenger systems activated upon somatostatin binding to the receptor. The signaling pathways coupled to the different SSTR subtypes have been studied extensively. Indeed, somatostatin binding to SSTR subtypes in native membranes results in modulation of a wide range of second messenger systems through the stimulation of different types of G proteins (29, 30). The diversity of the transduction pathways reflects the pleiotropic actions of the receptors. The presence of multiple SSTR subtypes in the various cells and tissues made it difficult to assign particular transduction pathways to single receptors. Thus, the study of recombinant receptors expressed in appropriate cell lines and the use of SSTR subtype-selective agonists and antagonists has helped in overcoming this problem.

The most important systems of SSTR signaling include the inhibition of adenylyl cyclase activity and modulation of the activity of potassium and calcium channels, mostly involved in modulation of secretion processes, as well as stimulation of phosphotyrosine phosphatase (PTP) or MAPK activity, mostly involved in control of cell growth and differentiation (23–26). It is noteworthy that involvement of the ERK system has been reported in the complicated mechanisms through which SSTR control cell proliferation (28).

1. Adenylyl cyclase activity

Adenylyl cyclase is one of the first identified effector proteins associated with an activation of SSTR (31). The SSTR subtypes are generally negatively coupled to adenylyl cyclase in different cells, although human sst_5 expressed in the presence of elevated concentrations of selective agonists can also induce its activation in specific cell systems (29).

2. Ion channel activity

The modulation of ion channels represents an additional common mechanism through which SSTR subtypes transfer their messages into the cells; this mechanism mostly involves potassium and calcium channels. Indeed, SSTR can directly mediate the activation of different types of potassium channels, either in a stimulatory or in an inhibitory manner (29). SSTR can also be associated with an indirect modulation of potassium channels, through the activation of phospholipase A_2 and consequent production of arachidonic acid, whose metabolites activate potassium currents. Alternatively, SSTR can indirectly modulate potassium channels through the stimulation of phospholipase C (PLC) signaling system, which can cause a change of potassium channel activity and consequent calcium concentrations (29). An additional major signaling pathway associated with SSTR is represented by the inhibition of voltage-dependent calcium channels, which has been demonstrated for several SSTR subtypes in different cell lines (30). It is noteworthy that the negative regulation of calcium currents represents one of the major mechanisms through which SSTR control GH release in GH-secreting pituitary cells (32).

3. PTP activity

The inhibition of PTP is one of the mechanisms through which SSTR mediate control of cell proliferation. Indeed, it has been demonstrated that sst_2 stimulation mediates an antiproliferative action in transfected cells through the coupling with a PTP activation pathway, whereas sst_5 mediates an inhibition of cell growth through coupling to the PLC inhibitory pathway (33).

Another type of PTP, the receptor-like membrane PTP, r-PTPeta, also mediating an antiproliferative effect, has been identified; the activation of this PTP causes an inhibition of MAPK activity and a stabilization of the cell cycle inhibitor $p27_{kip1}$ (34). It is important to mention that SSTR has been described to also interact with serine/threonine phosphatases. Indeed, a modulation of N- and L-type calcium channels and potassium channels depending upon an activation of protein phosphatase 2A and 2B, or calcineurin, has been demonstrated in different cell types, including pituitary tumor cells (29).

d. MAPK activity

The MAPK signaling system is another mechanism of control of cell proliferation associated with SSTR (23–26). SSTR may induce an antiproliferative effect in different cell systems either inhibiting or activating MAPK system.

In fact, although the activation of MAPK system is thought to be required for promoting cell growth in many cell types, it has been demonstrated that stimulation of different mediators of the MAPK pathway via distinct SSTR subtypes can also be associated with growth inhibition (35). The stimulation of sst_2 caused an inhibition of cell proliferation, presumably via the activation of ERK and MAPK cascade member p38 (36). Moreover, sst_4 has been shown to mediate antiproliferative effects via the stimulation of p38 that results in an activation of the cyclin-dependent protein kinase inhibitor p21cip1/WAF1 (36). Furthermore, the activation of sst_1 caused an arrest of cell growth and suggested that at least some of the antiproliferative effects were mediated through a prolonged activation of ERK and a resulting induction of p21cip1/WAF1 (37). It has been proposed that SSTR-coupled inhibition or activation of different MAPK cascade members is mediated by PTPs (34, 35, 37, 38).

It is noteworthy that SSTR are demonstrated to inhibit cell proliferation through a cell cycle arrest in G_1. Indeed, in studies performed in cells stably expressing transfected sst_2 and sst_5, somatostatin caused cell cycle arrest in G_1 due to up-regulation of cyclin-dependent kinase inhibitors, including p27kip1 (39). Moreover, a more recent study showed a significant increase in p27 expression by both sst_2 and sst_5 selective analogs in somatotroph tumors, confirming the role of p27kip1 in mediating the somatostatin effect on the inhibition of cell proliferation in GH-secreting pituitary tumors (40, 41). On the other hand, it has been found recently in cells expressing sst_2 and sst_5 that the sst_2 activation by a selective agonist was more efficacious at inhibiting adenylate cyclase, activating ERK1/2, and inducing the p27Kip1 in cells expressing both sst_2 and sst_5 compared with SSTR2 alone, suggesting that a cooperation of both receptors, probably represented by the heterodimerization, is important for the amplification of this mechanism and the consequent significant inhibition of cell proliferation (40, 41).

The antiproliferative effect mediated by SSTR can also be a consequence of apoptosis. In cell lines, sst_3 (but not other SSTR subtypes) induces apoptosis through a mechanism involving an induction of p53 (42). In contrast to this statement, it has been reported that sst_2 induces apoptosis independently from the accumula-

tion of p53 in a different cell line (43). Moreover, sst_2 was found to cause apoptosis via two different mechanisms, namely the down-regulation of mitochondrial Bcl-2 protein expression and the up-regulation of the expression of death receptors belonging to the TNF family (44).

In general, direct antiproliferative effects of somatostatin are mainly mediated via a transduction pathway involving the coupling of SSTR to PTPs.

The SSTR subtypes sst_1, sst_2, sst_4, and $sstr_5$ mediate direct cytostatic effects, whereas sst_2 and sst_3 may be responsible for the apoptosis. It is noteworthy that the current understanding of SSTR subtype-selective signaling reflects a rather complicated picture. It is mostly based on experiments using receptors from different species expressed in different cell types.

The observation that receptor coupling to a given pathway may be strongly influenced by the ligand used in the different settings further increases the complexity of these mechanisms. Therefore, the presently available data should be interpreted with caution.

Table 1 summarizes the functional data related to SSTR. The signaling pathways of SSTR are shown in Fig. 1 (23, 45).

C. Somatostatin receptor expression in human pituitary gland

1. Normal pituitary

The SSTR expression has scarcely been studied in the normal pituitary. However, some studies have demonstrated that all five subtypes of SSTR are expressed in fetal normal pituitary, whereas four of the five SSTR remain expressed in the adult normal pituitary gland, where sst_4 seem to be lacking.

The exact role of SSTR has never been identified, although they are presumably involved in the physiological control of hormone release and cell growth (46).

2. GH-secreting pituitary tumors

Since 1985, the presence of membrane SSTR has been demonstrated through binding studies in GH-secreting human pituitary tumors (47). The SSTR subtype more commonly expressed in these tumors is sst_2, which is found in more than 95% of tumors; followed by sst_5, expressed in more than 85%; sst_3 and sst_1, both expressed in more than 40%; and finally sst_4, which has rarely been found in GH-secreting pituitary tumors (48, 49).

Recently, however, the quantitative evaluation of the SSTR subtypes expression has demonstrated that sst_5 is the more abundantly expressed subtype, followed by sst_2, sst_3, sst_1, and sst_4, in GH-secreting pituitary tumors (50). The predominant expression of sst_2 and the sst_5 forms the basis for the successful clinical application of the octapeptide SA, such as octreotide and lanreotide, displaying a high affinity for sst_2 and moderate affinity for sst_5 in the treatment of these tumors. These molecular findings explain the evidence that SA is rarely completely ineffective in GH-secreting pituitary tumors (51).

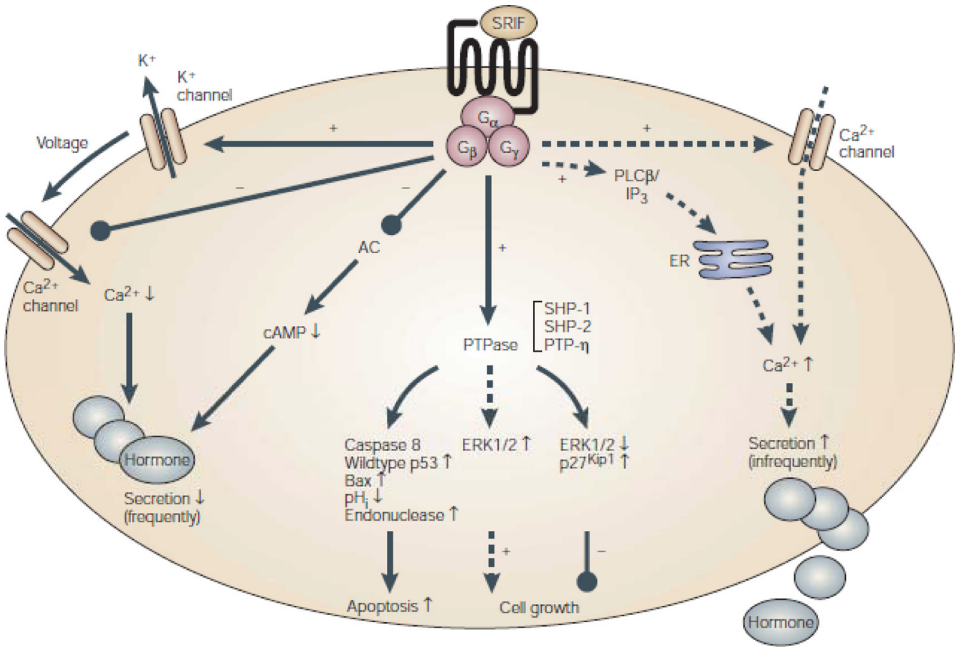

FIG. 1. Schematic representation of the most important SRIF-mediated signaling cascades leading to changes in hormone secretion, apoptosis and cell growth. In most cells, SRIF inhibits hormone as well as other secretions and plays a role in the control of cell growth and apoptosis. In a G protein-dependent manner, PTPases are activated, leading to dephosphorylation of signal-transducing proteins. SRIF-induced inhibition of ERK1/2 blocks degradation of the cyclin-dependent kinase inhibitor p27kip1, leading to growth arrest. AC, Adenylyl cyclase; ER, endoplasmic reticulum; Gα, Gβ, Gγ, G protein subunits; IP3, inositol trisphosphate; pH_i, intracellular pH; PTPase, phosphotyrosine phosphatase. [Derived from Ref. 45. Copyright obtained.]

Moreover, conversely to normal GH secretion showing tachyphylaxis after continuous receptor activation within hours to days, pathological GH secretion by SSTR-positive GH-secreting pituitary tumor cells can be inhibited during significantly prolonged periods (51). Indeed, escape from SA therapy has not been observed in this type of patient, even after many years of continuous treatment (52). The only reported exceptions were a single case of acromegaly showing complete desensitization to octreotide (53) and another case of partial tachyphylaxis to SA, where changes in receptor function or signal transduction cascade (rather than changes in receptor expression) were hypothesized (54).

D. Molecular basis of resistance to somatostatin analogs in GH-secreting pituitary tumors

The molecular basis of the different sensitivity of GH-secreting pituitary tumors to SA has been widely investigated over the last 10 yr. The different hypotheses raised to explain the variable sensitivity or resistance of these tumors to SA mainly include: 1) absence or reduced density of SSTR with high affinity for SA or the heterogeneous expression of SSTR within the tumors; 2) the mutation of gene encoding for SSTR leading to the absence of functional receptors; and 3) desensitization of SSTR for the uncoupling to the signaling cascade (51).

1. Impairment or heterogeneity of SSTR expression

The most recognized hypothesis explaining the resistance to SA in GH-secreting pituitary tumors is the absence or reduced density of SSTR, especially sst_2 and/or sst_5 in the tumor. Indeed, a quantitative loss of SSTR, evaluated by binding studies, was reported in relation to the very poor or absent GH suppression in response to acute administration of somatostatin or octreotide (55). However, such a loss of SSTR is seldom encountered and cannot fully explain the partial GH-suppressive effects of octreotide and SR in the treatment of patients bearing these tumors. In another study on a large series of GH-secreting pituitary tumors, the *in vitro* density of SSTR was poorly correlated with the *in vitro* effect of octreotide on GH suppression (56).

However, a recent study has shown a significant correlation between the absence of sst_2 expression, evaluated by immunohistochemistry, and the absence of *in vivo* hormonal response to SA in patients with GH-secreting pituitary tumors (57). Moreover, a recent study evaluating the quantitative expression of SSTR at molecular levels demonstrated that the amount of sst_2 gene product was positively correlated with the *in vivo* hormonal and tumor response in patients with GH-secreting pituitary tumors (58). An independent study also demonstrated the existence of a positive correlation between sst_2 expression, at the protein level, and *in vitro* GH suppression or *in vivo* IGF-I control (59). These studies support the thesis of a pivotal role of sst_2 expression in the development of sensitivity or resistance to SA. On the other hand, some studies have focused attention on sst_5 also. In fact, sst_5 has been hypothesized to be essential for the SA-induced hormonal control in GH-secreting pituitary tumors. This seems to be related to the evidence that the activation of sst_2 and sst_5 results in a synergistic effect on GH release (60) and to be supported by the observation that these two receptors may form heterodimers with enhanced functionality (61).

The finding that sst_5-preferential agonists have been shown to induce a significant inhibition of GH release in several GH-secreting tumors (62) supports the hypothesis that the involvement of sst_5 is important for the inhibition of GH release at least in a proportion of GH-secreting pituitary tumors. In this respect, an absent or scant expression of sst_5 may account for the reduced sensitivity or resistance of a group of GH-secreting pituitary tumors to SA.

Recently, the activation of sst_1 by the sst_1-selective agonist has been found to induce a dose-dependent inhibitory effect on GH secretion and a decrease in cell viability in GH-secreting pituitary tumors (63). In our experience, an sst_1-selective agonist was able to significantly suppress *in vitro* GH secretion in tumor cells derived from patients poorly sensitive to LAR or SR (64). The totality of this evidence suggest that the resistance to SA may be dependent on tumors' rearrangement of receptor pattern.

Beyond the lack of specific SSTR subtypes with high affinity for octapeptide SA, a nonhomogeneous distribution of these receptors has been found in a subset of human GH-secreting pituitary tumors (65). This suggests that poor sensitivity to SA, especially for a secondary development of resistance, might be due to the outgrowth of tumor cell clones, which may still express SSTR, albeit of the subtype to which the current generation of octapeptide SA do not bind. However, this phenomenon does not seem common in GH-secreting pituitary tumors.

2. Mutation in SSTR genes

Few data are presently available with respect to SSTR gene mutations leading to a loss of function. In a series of 19 human GH-secreting pituitary tumors with variable sensitivity to SA treatment *in vivo*, no mutations in sst_2 and sst_5 genes were found in any tumor (66). Similarly, no mutations in sst_2 gene were detected in a series of 15 GH-secreting pituitary tumors (67).

These data suggest that gene mutations on SSTR subtypes, at least the most frequently expressed sst_2 and sst_5,

are not at the basis of the resistance of GH-secreting pituitary tumor to SA. However, Ballarè *et al.* (68) described a germ line mutation (Arg240Trp) in the sst_5 gene in an acromegalic patient resistant to SA treatment; this mutation results in decreased inhibitory effect of SRIF on adenylate cyclase activity and increased MAPK activity so that cells transfected with the mutant sst_5 displayed increased proliferation compared with wild-type cells. This evidence suggests that this specific mutation in $sstr_5$ abrogates the antiproliferative action and activated mitogenic pathways.

Another study has recently evaluated the presence of polymorphisms in sst_2 and sst_5 and correlated it to the sensitivity to SA in 66 patients with GH-secreting pituitary tumors; the results of this study demonstrated that none of the three sst_2 gene polymorphisms evaluated played a role (69). Conversely, two different polymorphisms of sst_5 gene (t-461c and c1004t), of the three evaluated, were associated with resistance to SA, confirming the important role of sst_5 in determining the sensitivity of GH-secreting pituitary tumors to SA (69).

3. Decreased sensitivity of SSTR proteins

A potential mechanism of resistance of GH-secreting tumors to SA may be represented by the decreased sensitivity of SSTR due to receptor uncoupling with the intracellular signaling system.

A G protein gene mutation, which prevents G protein coupling with the receptors has been hypothesized as a possible cause of SSTR decreased sensitivity. Indeed, G protein mutations, particularly mutations in Gsα, have been shown to be associated with overproduction of hormones by pituitary-derived tumors, as well as with pituitary hyperplasia (70). In a subgroup of patients with GH-secreting pituitary tumors, elevated basal adenylyl cyclase activity and poor responsiveness to stimulatory agents such as GHRH (growth hormone releasing hormone) suggested constitutive activation of the adenylyl cyclase cascade in tumor cells.

A considerable number of these tumors contained an activating mutation in Gsα, which correlated with a higher sensitivity to SA that was not explained by the increase in sst_2 expression (71). Beyond this experience, the possibility that mutations of one or more factors involved in the signaling of SSTR can be responsible for receptors' decreased sensitivity and SA resistance in GH-secreting tumors cannot be excluded. Beyond a peculiar pattern of SSTR expression, alteration in specific factors of the signaling cascade may be responsible for the rare cases of resistance selectively involving the secretory process or the antiproliferative effects. Indeed, a dissociation between the antisecretory and antiproliferative action of SA and the consequent selective resistance has been demonstrated in patients with GH-secretory pituitary tumors (72, 73).

III. Pharmacology of Currently Available Somatostatin Analogs

The expectation that SRIF would be of therapeutic value in clinical conditions was based on its ability to inhibit many functions of various organs (74). However, clinical use of native SRIF was hampered by the need for iv administration, its short duration of action (a half-life in the circulation of less than 3 min), and the postinfusion rebound hormone hypersecretion (GH, insulin, and glucagon) (75).

The shortcomings of native SRIF to be used in clinical practice have prompted the synthesis and experimentation of a number of synthetic analogs that do not have these disadvantages.

Synthetic SA with longer half-lives have therefore been developed for therapeutic use, and their main indications are summarized in Table 2. For example, octreotide, which has high affinity for sst_2 receptors and weak and moderate affinity for sst_3 and sst_5, respectively, in the sc formulation has a half-life of 90 to 120 min (76, 77). Octreotide is approved for and has proven efficacy in the treatment of a number of conditions because it inhibits the release of insulin, glucagon, TSH, and vasoactive intestinal peptide and has many other functions (78).

A long-acting release depot formulation of octreotide (LAR), which provides sustained exposure after im injection every 28 d, has been developed and is approved for use in clinical practice. The safety/tolerability profile and the

TABLE 2. Established, probable, and possible indications for the use of SA

Established indications	Pituitary adenomas secreting GH or thyrotropin after unsuccessful surgery or with clinical conditions that prevent safe surgery
	Metastatic islet-cell tumors, especially vipomas and glucagonomas
	Metastatic carcinoid tumors
	SSTR scintigraphy of SSTR-positive diseases
Probable indications	Acute esophageal variceal bleeding, especially if sclerotherapy is not available or has failed
	Pancreatic and enteric fistulas
	Prevention of complications after elective pancreatic surgery
	Secretory diarrhea
	AIDS-related diarrhea
Possible indications	Other SSTR-positive neuroendocrine tumors and adenocarcinomas
	Upper gastrointestinal bleeding
	Pancreatitis induced by endoscopic retrograde cholangiopancreatography

Modified from Ref. 72.

pharmacokinetic (PK) characteristics of this long-acting octreotide formulation are well defined and have been assessed in numerous clinical trials for more than a decade (78). Lanreotide, another SA that binds to sst_2 and sst_5, is also available in a prolonged-release formulation. At variance with LAR, fewer published data assessing lanreotide (SR and ATG) are available, although the safety/tolerability profile and PK properties of this agent have been reported (79). Indications for treatment with lanreotide are the same as those with octreotide (Table 2).

The pharmacological properties of the currently available SA for treatment of pituitary and neuroendocrine tumors and of those expected to be available in the future are briefly reviewed in this section.

A. Octreotide sc and long-acting repeatable

Octreotide, the first SA used in clinical practice, was introduced in the early 1980s to overcome the 2-min half-life of native somatostatin (75). In a single-dose study, performed to examine the PK of octreotide in acromegalic patients and to investigate the relationship between GH and the elimination half-life of the drug, Nicholls *et al.* (76) studied 14 patients with acromegaly. Octreotide 100 μg was administered sc. Plasma samples were taken every 10 min for 1 h, and then hourly for up to 8 h; GH was measured at 0, 2, and 8 h. Octreotide was rapidly absorbed with a mean (±SEM) half-life of 5.4 min (±0.8), peaking at a mean plasma concentration of 3.4 nmol/liter (±0.2) in 27.4 min (±3.7). The monoexponential elimination phase had a mean half-life of 100–120 min (110 ± 9.6 min). The apparent volume of distribution was 29.4 ± 1.9 liter, and total clearance was 172 ± 10.4 ml/min. These results were similar to those obtained in normal volunteers (77). The relationship between GH levels and octreotide half-life was not simple (76).

Currently, octreotide is not used anymore for chronic treatment in acromegaly, unless the long-acting SA formulations are not available. After the first report by Lamberts *et al.* (80) that single administration with 50 μg octreotide was helpful to predict the response to 12-month treatment, thus sparing poorly responsive patients the long-term treatment, other authors have provided similar results with a dosage of 100 μg or iv administration (81–85). However, some other experiences did not support routine use of an acute test with octreotide to predict long-term response to LAR or lanreotide (86–88), and this test is not generally used. We found that an acute test with 100 μg octreotide given sc had a high positive but poor negative predictive ratio (86). Therefore, we proposed to use the acute test only to verify the gastrointestinal tolerability to SA (86).

LAR comprises a biodegradable polymer matrix, from which octreotide is released in a biphasic manner (78). In patients with acromegaly, within 1 h of a single im dose of octreotide LAR 10–30 mg, an initial peak in serum octreotide concentrations occurred, presumably from drug adsorbed to the carrier microspheres. This initial peak, which coincided with an 8- to 12-h period of GH suppression, is limited to 0.5% of the total area under the drug concentration-time curve for d 0–60 (89). Serum octreotide concentrations declined within 12 h of drug administration, remaining subtherapeutic until d 7 before increasing in a dose-dependent manner to plateau at about d 14 (89). The plateau concentration remained stable until d 35–60 and then steadily declined. Peak serum concentrations were dose dependent and were reached in 28–34 d. Octreotide concentrations reached steady state after three im injections of LAR at 4-wk intervals. Therapeutic drug concentrations (usually 1000–3000 ng/liter) were maintained throughout the plateau phase in patients receiving LAR 20 or 30 mg; suppression of GH secretion was maximal (levels reached 2–5 μg/liter) during this period. Bioavailability after 20- or 30-mg doses is 39 or 50% relative to the sc formulation (89).

Distributed mainly to the plasma, octreotide is 41–65% protein bound. In patients with acromegaly, the volume of distribution is 18–30 liter (after an iv dose of 25–200 μg). Hepatic extraction is believed to be extensive (30–40%), and approximately 11–32% of the administered drug is eliminated unchanged in the urine. The elimination half-life of octreotide is 1.7 h. Total body clearance is approximately 10 liter/h in healthy volunteers, 18 liter/h in patients with acromegaly, and 4.5 liter/h in patients with chronic renal failure.

In sequential clinical trials, once-monthly LAR im administration (usually 20 or 30 mg once monthly) provided continued efficacy after a prior regimen of octreotide sc (300–600 μg/d) administered three times daily (90–94).

B. Lanreotide slow-release and autogel

Similar to octreotide, lanreotide is an octapeptide analog of SRIF that acts as a specific and potent agonist of sst_2 and sst_5.

The selective affinity of lanreotide for these receptor subtypes confers a relative specificity of action on GH secretion and makes lanreotide suitable for the treatment of acromegaly. The first formulation of lanreotide available to treat patients with acromegaly was the SR that is a microparticle form (79). SR includes classical formulations (10–30 mg) given every 10–14 d and a more recent formulation (60 mg) that can be given every 21–28 d. Lanreotide ATG, consists of a solution of lanreotide in water with no additional excipients administered every 28–56 d by deep sc injection from a prefilled syringe (95). This provides an extended dosing

interval compared with the microparticle lanreotide formulation, which requires injection every 7–14 d. ATG was found to have linear PK for the 60- to 120-mg doses and provided a prolonged dosing interval and good tolerability. In patients with acromegaly, after single and repeated injections, the time (Tmax) to reach peak serum concentrations (Cmax) appeared to be independent from the dose over the range 60–120 mg, with no statistically significant differences by dose when Tmax values were compared (95). The dosage range was 60–120 mg every 28–56 d (95). SR was initially used in patients previously treated with octreotide and showed successful control of GH and IGF-I excess in those patients previously responsive to the drug, and even in some others not fully controlled (96–101). Only limited data are available with the 60-mg dosage of the SR formulation (102). Similarly, ATG has been shown to be efficient in patients previously treated with the SR formulation as well as in patients treated first-line.

Detailed data on the efficacy of all formulations in acromegaly are reported in *Section IV*. Efficacy of LAR and ATG are reportedly similar (103), even if LAR had a more predictable PK profile than ATG (104).

IV. Resistance to Somatostatin Analogs

Before a definition of resistance to SA in acromegaly is discussed, it is appropriate to revise the definition of disease activity and the reported prevalence in the literature of response to these drugs.

In line with Giustina *et al.* (8), during or after any therapy, acromegalic patients can be classified according with these categories: 1) well controlled, when GH nadir after glucose load is below 1.0 μg/liter in the presence of normal IGF-I levels adjusted for age and gender and no clinical activity; 2) inadequately controlled, when GH nadir after glucose load is above 1.0 μg/liter in the presence of elevated IGF-I but absence of clinical activity; and 3) poorly controlled, when GH nadir after glucose load is above 1.0 μg/liter in the presence of elevated IGF-I and overt clinical activity.

Although it is generally accepted the need of categorization of patients with acromegaly according with their disease activity, the above-mentioned categories have two major limitations: GH assay and cutoff validity, and the difficulty in evaluating clinical disease activity in a condition such as acromegaly characterized by a long-estimated disease duration and often scant clinical symptoms.

It is a fact that GH nadir cutoff after OGTT has been reported to be inadequate, and even confounding, to define remission of acromegaly in patients undergoing treatment with SA (105). Moreover, GH levels depend on several factors, including the sensitivity of the assay and the patients' age, gender, and body mass index (BMI), so that a definition of response on the basis of biochemical data is still to be clarified (106, 107).

Even considering that a definition of resistance to SA treatment based only on GH and IGF-I response is limited, data currently available report only on this biochemical criterion after treatment with octreotide, LAR, SR, or ATG as a single agent or (more frequently) as a sequential use of more than one SA, with variable doses, and for a generally short period of treatment, rarely exceeding 12 months. To provide a meaningful definition of resistance to SA, it is essential to define the rate of response to individual SA.

A. The outcome of treatment with somatostatin analogs in clinical practice

This section reviews the studies reporting on outcome of SA in terms of GH and IGF-I control and tumor shrinkage. A search for original articles, published between 1990 and 2009 and focusing on octreotide and lanreotide in acromegaly, was performed in MEDLINE and PubMed. The search terms used were "acromegaly," "pituitary adenoma," "octreotide," and "lanreotide."

Exclusion criteria for this analysis were: inclusion of fewer than 10 patients, duration of treatment shorter than 12 months, use of more than one single SA to avoid the cumulative effect with the previous drug (but use of octreotide for $\leq$3 months was not considered an exclusion as well as a washout period from previous treatment of $\geq$3 months), and full text not available. This latter criterion was chosen to have a clear definition of treatment response to calculate the response rate. Our personal experience on published data and unpublished results has been included in *Section IV.A.5*.

1. Octreotide sc

Of 73 papers found by using "acromegaly and subcutaneous octreotide" as key words, five (108–112) fulfilled our criteria for analysis (Table 3). A total of 508 patients have been treated with octreotide alone, with dosages ranging from 50–1500 μg/d for 12 months; control of GH and IGF-I levels was achieved in 18% (10–25%) of 319 patients and 49% (37–68%) of 349 patients, respectively. Tumor shrinkage was reported in 36% (29–50%) of 190 patients.

2. Octreotide LAR

Of 125 papers found by using "acromegaly and octreotide LAR" as key words, 11 (113–123) fulfilled our criteria for analysis (Table 4). A total of 956 patients have been treated with variable doses of LAR (10–40 mg monthly) for 12–108 months; control of GH and IGF-I

TABLE 3. Effects of sc octreotide in acromegaly

First author, year (Ref.)	No. of patients	Treatment		Treatment outcome, n (%)		
		Maximal duration (months)	Dose (μg/d)	GH levels ≤2.5 μg/liter	Normal IGF-I for age	Tumor reduction >20% of baseline
Sassolas, 1990 (108)	58	12	300–1500	12 (21)	Not shown	13/38 (34)
Vance, 1991 (109)	189	12	100–1500	Not shown	46/99 (46)	15/34 (44)
Ezzat, 1992 (110)	98	12	100–750	21 (21)	67 (68)	20/70 (29)
Ezzat, 1995 (111)	99	12	50–1500	10 (10)	36 (37)	8/23 (35)
Arosio, 1995 (112)	64	12	300	16 (25)	21/53 (40)	13/25 (50)
Total	508		50–1500	59/319 (18)	170/349 (49)	69/190 (36)

The criteria for selection of studies are detailed in *Section IV.A*.

levels was achieved in 60% (37–72%) of 900 patients and 59% (34–75%) of 956 patients, respectively. Tumor shrinkage was reported in 70% (9–88%) of 627 patients.

3. Lanreotide SR

Of 116 papers found by using "acromegaly and lanreotide" as key words, seven papers (100–102, 124–127) fulfilled our criteria for analysis (Table 5). A total of 474 patients have been treated with SR at variable doses of 60–120 mg every 4 wk for 12 months; control of GH and IGF-I levels was achieved in 57% (31–78%) and 56% (35–72%), respectively, of 474 patients. Tumor shrinkage was reported in 22% (8–39%) of 210 patients.

4. Lanreotide ATG

Of 39 papers found by using "acromegaly and lanreotide Autogel" as key words, five (128–132) papers fulfilled our criteria for analysis (Table 6). A total of 264 patients were treated with ATG at dosages ranging from 60–120 mg every 14, 21, 28, or 56 d for 12 months; control of GH and IGF-I levels was achieved in 62% (54–85%) and 49% (37–59%), respectively, of 264 patients. Data on tumor shrinkage in patients treated with ATG are still very scant and pertain to only two studies (130, 132). Attanasio *et al.* (128) reported shrinkage in 73% of 22 patients, similar to our experience (132) showing more than 25% decrease of tumor mass compared with baseline in 77% of 26 patients.

5. Personal experience

Similar to the previous section, we reviewed our experience reporting the results of our published studies, which fulfilled criteria stated above (Table 7). All studies that included patients enrolled in multicenter studies are reported in *Sections IV.A.1–4*. Of 253 patients included in seven studies (133–139) and treated with octreotide, LAR, SR, or ATG, control of GH and IGF-I levels was achieved in 70 and 67%, respectively, and tumor shrinkage in 87% of patients after 12–60 months. As shown in Fig. 4, the outcome of response in our personal experience increases over time. Clearly, the 100% control of GH and IGF-I and greater than 25% tumor shrinkage in the patients treated for 5 yr (Fig. 2, *top right*) do not refer to a true result but are due to the fact that only the responsive patients could have received exclusive SA treatment for a long period without any other approach if not entirely controlled. If

TABLE 4. Effects of octreotide LAR in acromegaly

First author, year (Ref.)	n	Maximal duration (months)	Dose (mg/q 28 d)	GH levels ≤2.5 μg/liter, n (%)	Normal IGF-I for age, n (%)	Tumor reduction >20% of baseline, n (%)
Davies, 1998 (113)	12	12	20–40	6 (50)	7 (60)	2 (17)
Lancranjan, 1999 (114)	149	12	10–30	104 (70)	98 (66)	Not shown
Cozzi, 2003 (115)	110	48	10–30	79 (72)	82 (75)	38/83 (46)
Ayuk, 2004 (116)[a]	91	12	10–30	61 (67)	48 (72)	Not shown
Jallad, 2005 (117)	57	24	10–30	32 (56)	20 (36)	19/25 (76)
Cozzi, 2006 (118)	67	108	10–30	46 (69)	47 (70)	55 (82)
Mercado, 2007 (119)	68	12	10–30	30 (44)	23 (34)	51 (75)
Valentim, 2008 (120)	276	24	20–30	157 (57)	185 (67)	243 (88)
Oki, 2009 (121)	30	24	10–40	11 (37)	16 (53)	Not shown
Colao, 2009 (122)[b]	40	12	20–30	16 (40)	16 (40)	29 (73)
Ghigo, 2009 (123)	56	12	20–40	Not shown	19 (34)	5 (9)
Total	956		10–40	542/900 (60)	561/956 (59)	442/627 (70)

The criteria for selections of studies are detailed in *Section IV.A*.

[a] The prevalence of IGF-I control was reported for 67 patients only.

[b] This study is included here because it presents results of a multicenter study.

TABLE 5. Effects of lanreotide SR in acromegaly

First author, year (Ref.)	No. of patients	Treatment		Treatment outcome, n (%)		
		Maximal duration (months)	Dose (mg/q 28 d)	GH levels ≤2.5 μg/liter	Normal IGF-I for age	Tumor reduction >20% of baseline
Giusti, 1997 (124)	57	12	60	31 (54)	20 (35)	Not shown
Baldelli, 2000 (100)	118	12	60–90	92 (78)	82 (70)	10 (8)
Chanson, 2000 (125)	58	12	60–90	24 (41)	24 (41)	Not shown
Verhelst, 2000 (101)	66	12	60–90	30 (45)	29 (44)	Not shown
Attanasio, 2001 (126)	57	12	60–90	29 (52)	41 (72)	Not shown
Attanasio, 2003 (102)	92	12	60–120	58 (63)	60 (65)	36 (39)
Karavitaki, 2008 (127)	26	12	30–120	8 (31)	11 (42)	Not shown
Total	474			272/474 (58)	267/474 (56)	46/210 (22)

The criteria for selection of studies are detailed in *Section IV.A*.

we compare only the SA outcome after 12 and 24 months, a trend toward a higher disease control in the second year of treatment is found (Fig. 2). This agrees with other studies reporting similar findings (115, 118, 140). However, it should be considered that the dosage is generally increased with treatment continuation so that final outcome depends on a cumulative drug effect over time and increased dosages, a combined effect that is impossible to verify in studies reporting data of short-term treatments. It is evident that higher dosages are associated with better responses, as documented at least with LAR (137, 141).

Thus, by limiting the analysis of SA outcome in terms of GH and IGF-I control to the results of a 12-month treatment, which generally represents a period of observation of the patients before any other treatment strategy is applied, and limiting it to LAR and ATG, which are the formulations currently used, we found that control of GH excess was obtained in 60 and 62% of patients, with normalization of IGF-I levels in 51 and 49% of patients, respectively (Fig. 3). Similar data on GH and IGF-I control have been reported in two other critical analyses of the literature (103, 142). Tumor shrinkage, evaluated as at least 20% tumor reduction compared with baseline, was observed in 56 and 75% of patients treated with LAR or ATG, respectively (Fig. 4). It should be mentioned that tumor shrinkage is greater in patients treated first-line than in those treated after unsuccessful surgery (20). Thus, tumor shrinkage might be considered as a marker at least in those patients treated first-line.

Thus, it is possible to infer that a biochemical response might be achieved in half of the patients within 12 months from the beginning of treatment, whereas an additional 25% of patients might be considered as responsive to the treatment based on tumor response if treated first-line. Alternatively, we can infer that only 25% of all treated patients with acromegaly presented neither a biochemical nor a tumor response after 12 months of treatment and might be defined as poorly responsive or resistant (Table 8).

B. Predictors of response

1. Molecular predictors

This topic has been detailed in *Section II.D*. To summarize, the expression of an adequate amount of SSTR on tumor cell membranes, in particular of sst_2 and sst_5, is a recognized prerequisite for response, even if the correlation between receptor expression and clinical response is not perfect (55, 58, 59).

2. Biology

Different mutations have been identified in densely and sparsely granulated GH-secreting pituitary tumors. Indeed, gsp mutations were identified in densely granulated somatotroph adenomas, which have high adenylate cy-

TABLE 6. Effects of lanreotide ATG in acromegaly

First author, year (Ref.)	No. of patients	Treatment		Treatment outcome, n (%)		
		Maximal duration (months	Dose (mg/q 28 d)	GH levels ≤2.5 μg/liter	Normal IGF-I for age	Tumor reduction >20% of baseline
Attanasio, 2008 (128)	26	12	60–120	11 (42)	14 (54)	16/22 (73)
Chanson, 2008 (129)	62	12	60–120	53 (85)	24 (38)	Not shown
Colao, 2009 (130)	26	12	60–120	14 (54)	14 (54)	20/26 (77)
Melmed, 2010 (131)	99	12	60–120	53 (54)	58 (59)	Not shown
Lombardi, 2009 (132)	51	12	120	32 (63)	19 (37)	Not shown
Total	264		60–120	163 (62)	129 (49)	36/48 (75)

The criteria for selections of studies are detailed in *Section IV.A*.

TABLE 7. Personal experience with SA in acromegaly

Ref.	Drug	No. of patients	Treatment duration (months)	Dose (mg q 28 d)		Treatment outcome, n (%)		
				Minimal	Maximal	GH levels ≤2.5 μg/liter	Normal IGF-I for age	Tumor reduction >25% of baseline
133	OCT	30	12	150 (μg/d)	Not stated	13 (43)	13 (43)	Not shown
134	SR	12	12	60	90	11 (92)	11 (92)	Not shown
135	SR	14	24	60	90	7 (50)	7 (50)	Not shown
136	LAR	36	12	20	30	24 (69)	17 (49)	20 (57)
136	LAR	28[a]	24	30	40	20 (71)	19 (68)	
137	LAR	56[b]	24	20	40	48 (86)	47 (84)	56 (100)
138[c]	LAR	30	12	10	30	16 (53)	16 (53)	26 (87)
138	SR	30	12	60	90	14 (45)	14 (47)	25 (83)
139[c]	LAR	28	60	20	40	27 (100)	27 (100)	27 (96)
139	SR-ATG	17	60	60	120	17 (100)	17 (100)	17 (100)
Total		281	12–60			197/281 (70)	188/281 (67)	171/197 (87)

The criteria for selection of studies are detailed in *Section IV.A*. Dose is expressed as milligrams every 28 d, except for Ref. 147, where units are micrograms per day. OCT, Octreotide.

[a] These patients were not included in the total patients because they were part of the 36 studied for 12 months.

[b] This series included the eight patients treated for 24 months published in a previous study (148).

[c] In these studies, the populations treated with either drug are shown separately.

clase levels, express the glycoprotein hormone α-subunit that is regulated by a cAMP response element, and respond to SA that reverse this intracellular environment (143–147). Conversely, sparsely granulated somatotroph tumors, which exhibit characteristic aggregation of cytoskeletal keratin filaments, harbor a somatic mutation in the GH-receptor that interferes with posttranslational processing, maturation, ligand binding, and signaling of the GH-receptor (148, 149). As a consequence, densely granulated adenomas, which are more likely to harbor Gs-α mutations, provide an intracellular target for SA inhibition, whereas the disruption of GH autoregulation by GH-receptor mutation in sparsely granulated adenomas renders GH-receptor antagonism a more appropriate

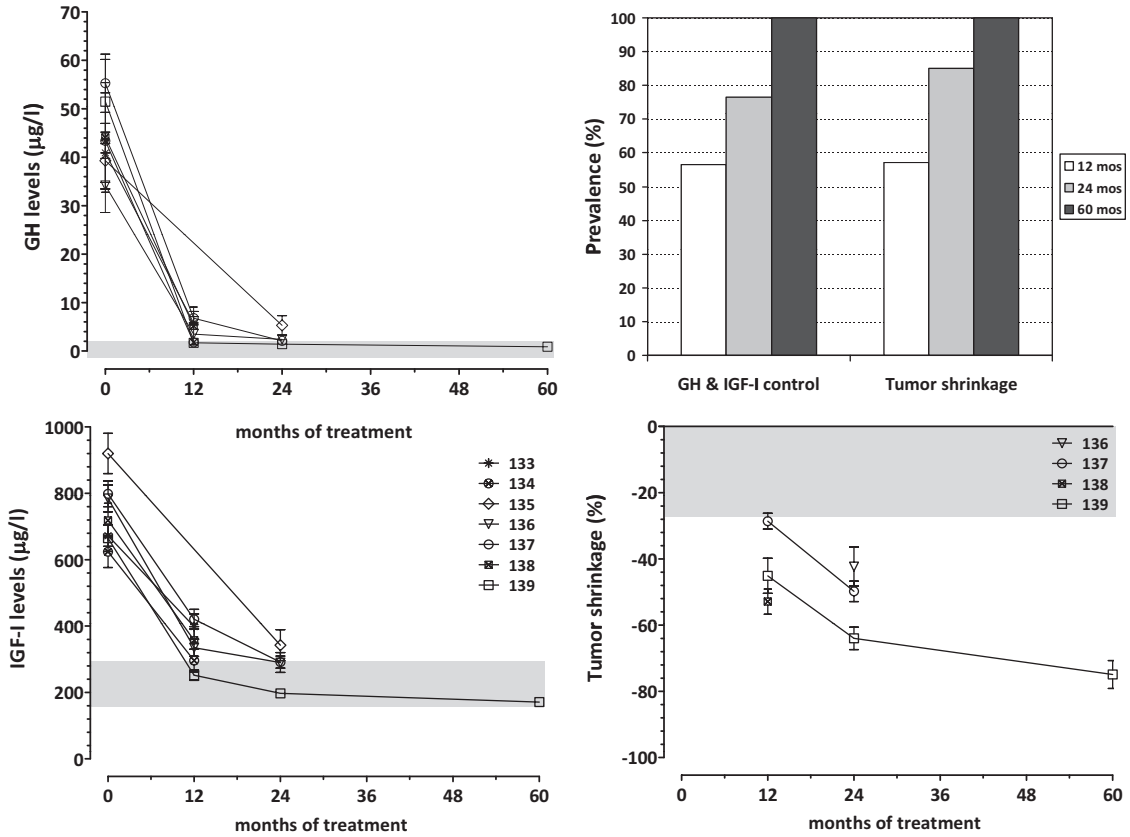

FIG. 2. GH profile (*top left*), IGF-I profile (*bottom left*), prevalence of disease control (*top right*), and tumor shrinkage (*bottom right*) in our experience. Data of treatment for 12, 24, and 60 months derive from studies reported in Table 8.

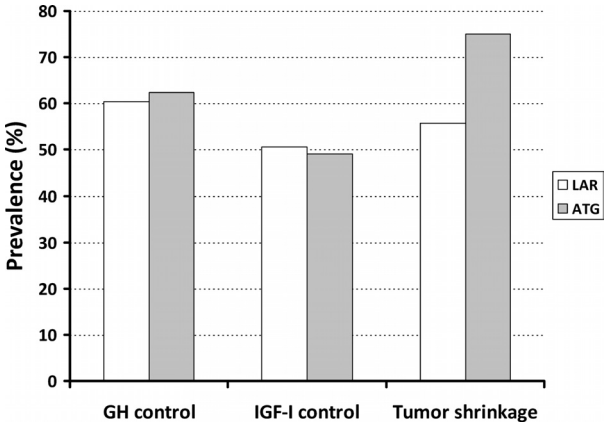

FIG. 3. Disease control obtained after 12-month treatment with octreotide-LAR (LAR) or lanreotide autogel (ATG). Data derive from studies reported in Tables 5–7. In detail, LAR results derive from a total of 482 patients included in Refs. 111, 112, 114, 117, 120, 121, 133 and 135. GH control was reported in 257 of 426 patients, IGF-I control in 244 of 482 patients, and tumor shrinkage in 115 of 206 patients. Data concerning ATG are all reported in Table 7.

TABLE 8. Definition of response to 12-month treatment of SA at therapeutic dosages in acromegaly

Full response	Control of GH and IGF-I levels and >20% tumor shrinkage in patients treated first-line Control of GH and IGF-I levels and >20% tumor shrinkage or stabilization of tumor remnant in patients treated second-line or in those with no tumor on magnetic resonance imaging at baseline
Partial response	Significant decrease (>50%) of GH and/or IGF-I levels with no achievement of control and/or >20% tumor shrinkage in patients treated first-line or second-line
Poor response or resistance	Nonsignificant decrease of GH and IGF-I levels with no achievement of control and no tumor shrinkage in patients treated first-line or increase in tumor size in any patient

therapeutic option less likely to be associated with treatment-induced tumor activation.

3. Clinical predictors

It is essential to mention that to restore life expectancy to normal it is mandatory that both GH and IGF-I secretion is reduced to levels comparable to the healthy population (150), even considering the difficulties in establishing the normative range and in analyzing the differences among different assays.

Some discrepancy has, however, been documented between GH and IGF-I levels, which appears to be a rather frequent phenomenon. In the Belgian registry enrolling 229 noncontrolled patients (151), one third of the patients had a discordant GH and IGF-I pattern. The high GH phenotype was found predominantly in younger estrogen-sufficient females, implying a possible role for age, gender, and estrogens in this biochemical divergence, whereas the high IGF-I phenotype was associated with a worse metabolic profile, suggesting that high IGF-I, rather than high GH, is indicative of persistently active disease. In a previous study, we also demonstrated that the addition of oral estrogens to young hypogonadal females receiving chronic SA treatment induced a significant reduction of IGF-I levels with a slight but significant increase of GH levels, so changing the relationships between the two parameters (152). Two other studies also suggested that estrogen-sufficient women or those receiving oral estrogens for hypogonadism might have elevated GH levels, both as a fasting sample (153) and after glucose load (154) in the presence of normal IGF-I levels.

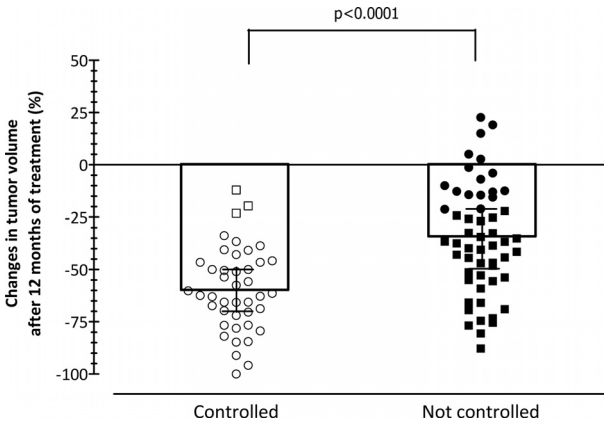

FIG. 4. Tumor volumes after 12 months of first-line LAR or lanreotide treatment in the 99 patients of Ref. 169. Results are shown as individual cases and mean ± SEM and by dividing the patients in two groups: 42 patients who achieved GH and IGF-I control (controlled) and 57 patients who did not (not controlled). ○, Patients with controlled GH and IGF-I levels and tumor shrinkage by at least 25% of baseline; □, patients with controlled GH and IGF-I levels and tumor shrinkage by less than 25% of baseline; ●, patients with noncontrolled GH and IGF-I levels and tumor shrinkage by less than 25% of baseline; ■, patients with noncontrolled GH and IGF-I levels and tumor shrinkage by at least 25% of baseline.

On the other hand, the existence of a gender difference in the relationship between serum GH and IGF-I is a well-known phenomenon (155). The results of several studies including our own experience (105, 106, 156–158) were again consistent with relative GH resistance observed in normal and GH-deficient females considered to be at least partly mediated by estrogens. Similarly, older patients generally have lower GH levels, both as fasting values or after glucose (156, 159, 160), and patients with a higher BMI have lower GH levels (154). Indeed, in patients older than 60 yr, cutoff GH levels as low as 1.4 μg/liter as fasting samples and 0.5 μg/liter as postglucose nadir levels were proposed (106). Nonetheless, no differences in GH levels according to age and gender were reported (157), but elderly patients have been shown to be more sensitive to SA

(159) and are diagnosed with a more severe cardiomyopathy than young patients (160).

The relations among multiple GH testing, GH nadir during OGTT, and IGF-I after surgery, after SA, or after DA treatment were analyzed in 166 patients (105); discordant results of GH nadir during OGTT were observed being 33, 48, and 18% in the three groups, respectively. In the patients studied during SA therapy, 42% of tests were discordant in terms of normal IGF-I and GH nadir greater than 1 μg/liter. No significant differences in discordance were observed when fasting GH levels were used, leading to the conclusion that both basal and GH nadir levels are highly discordant with IGF-I levels during SA therapy, and OGTT is not useful in assessing biochemical control in these subjects (105).

Prior surgery or radiotherapy was shown to have no effects on the GH response to SA, whereas radiotherapy was associated with less remarkable IGF-I percentage reduction (161).

One potential source of bias in analyzing GH values during treatment of acromegaly is the assay used itself. In fact, a recent study reported the results of measuring GH during a standard 75 g OGTT in 46 acromegaly patients and 213 healthy subjects using three different commercially available assays (Immulite, Diagnostic Products Corp., Los Angeles, CA; Nichols, Nichols Institute Diagnostika GmbH, Bad Vilbel, Germany; and DSL, Diagnostic Systems Laboratories, Sinsheim, Germany) that were calibrated against the recently recommended GH standards (106). Even if GH results from all assays were strongly correlated each other, GH levels obtained with the Immulite assay were, on average, 2.3-fold higher than those obtained with Nichols and 6-fold higher than those obtained with Diagnostic Systems Laboratories. Using cutoff limits of 1 μg/liter (Immulite) and 0.5 μg/liter (Nichols) identified 95% of patients with active disease and 78–80% of patients in remission (106). These authors confirmed that basal and nadir GH levels were significantly higher in females than in males and that age, BMI, and gender were all predictors for basal and nadir GH levels. This led to the conclusion that GH values should be assay, gender, age, and BMI specific (106). Therefore, currently used GH cutoff presents important drawbacks explaining the high rate of discrepancy with IGF-I levels and should be age-, gender-, and BMI-related to be appropriate as IGF-I ranges are. Moreover, there is also a need of individual cutoff limits for each assay.

As for the predictors of tumor shrinkage, no significant effect of post-SA treatment GH and IGF-I levels was reported in some studies (158, 162–167), whereas in several others biochemical control was significantly associated with tumor shrinkage and its amount (100, 112 168–170). Tumor growth during treatment with octreotide or SR was reported only in $\leq$ 2% of the patients (169, 170). Suppression of IGF-I levels after 12 months (169) and tumor shrinkage after 3 months (171) were major predictors of the amount of tumor shrinkage after 12 months of continuous SA treatment.

The initial tumor size does not seem to have an important role in subsequent shrinkage, although macroadenomas are more frequently reported to be reduced in size during SA treatment (mostly when administered first-line) than microadenomas (110, 115, 162, 164, 169), with one exception (163).

We can thus conclude that females who are of fertile age or receiving estrogen replacement (especially if taking oral estrogens) tend to have higher GH but lower IGF-I levels, and elderly patients tend to have smaller tumors and lower GH and IGF-I levels; these represent the two patient populations more likely to have IGF-I control and/or tumor shrinkage during SA. Young male patients are considered to have more difficulty in responding fully to initial SA treatment in terms of IGF-I normalization and tumor shrinkage because they frequently have more aggressive GH-secreting macroadenomas.

C. A definition of resistance

As previously reported, a clear definition of resistance to SA treatment in acromegaly is still missing. As proposed by Gola *et al.* (172), resistance to SA can be explained by combining the concepts of "biochemical resistance" and "tumor resistance." A detailed definition of these two latter conditions can be summarized as: 1) persistent basal GH excess associated to GH nadir greater than 1.0 μg/liter after OGTT and IGF-I levels above the normal range adjusted for age and gender as the "biochemical resistance"; and 2) increase in tumor size or a tumor shrinkage less than 20% compared with baseline volume as the "tumor resistance." Clearly, the definition of tumor shrinkage should be modified for patients treated first- or second-line, and duration and doses of SA should be appropriate before any definition of resistance is done; in fact, resistance to SA might not be defined before completion of at least 12 months of treatment, with adequate dosages, use of optimal GH and IGF-I assay, and results of biochemical measures corrected for patients' gender, age, and BMI.

Moreover, whereas biochemical and tumor responses are generally associated, there are some patients in which these responses are dissociated (72, 73).

In a previous study in which 99 patients were treated with either LAR or SR as first-line therapy for 12 months to investigate rate and predictors of tumor shrinkage (169), we found some dissociation between biochemical and tumor response (Fig. 4). Tumor shrinkage was greater in patients achieving biochemical control than in those

who did not, a finding rather expected (169). However, we also noticed that three patients (7%) who achieved disease control did not have any significant tumor shrinkage, arbitrarily established as at least 25% reduction in tumor volume compared with baseline, whereas 38 of the 57 patients who did not achieve disease control (67%) had tumor shrinkage during treatment (169). In these 38 patients, tumor shrinkage ranged from 26 to 77%. This suggests that a benefit of SA therapy can be observed even in the patients who do not completely control hormone excess if tumor shrinkage is analyzed as a marker of response. It is a matter of fact that tumor shrinkage is better evaluated in the patients treated first-line with SA than in those patients treated as second-line after unsuccessful surgery associated or not associated with radiotherapy (20). Thus, in the definition of resistance, the tumor response should probably be considered separately in the patients treated first-line and in those treated after surgery and/or radiotherapy.

Based on the foregoing, we suggest that response to SA is defined considering the biochemical and tumor response together after an adequate period of treatment and after dose optimization is performed in individual patients (Table 8).

It should also be mentioned that a subset of these poorly responsive patients might become responsive if the tumor mass is even partially removed by surgery (127, 173–175).

In a cohort of 86 patients followed in two independent centers in Italy (174) and not achieving biochemical control after first-line treatment with SA for at least 6 months, we demonstrated that surgical debulking of at least 75% contributed to GH and IGF-I control during a second course of SA in 56 and 55% of cases, respectively.

These data, together with some others (173, 175), indicate that a large initial tumor volume might be associated with an insufficient biochemical and/or tumor response, so defined as poor response, which in half of cases may be completely corrected by surgical removal of at least 75% of the tumor mass. In patients bearing large macroadenomas, it has thus been suggested (2, 176) that first-line treatment with SA is indicated to reduce hormone levels and reduce tumor mass, followed by surgery in the patients not fully responsive.

D. Therapeutic approaches for acromegalic patients resistant to somatostatin analogs

As previously mentioned, in about one third of acromegalic patients, SA treatment fails to induce adequate control of disease, where the persistence of GH and IGF–I excess in association with the persistence of the clinical syndrome suggest a still active disease.

In these cases, a more aggressive treatment is mandatory. Therapeutic approaches include pituitary surgery and/or radiosurgery to remove the tumor mass at least partially, as well as alternative medical treatment schedules based on the administration of high-dose SA, on the use of the GH-receptor antagonist pegvisomant as monotherapy, or on the association of SA with cabergoline and/or pegvisomant.

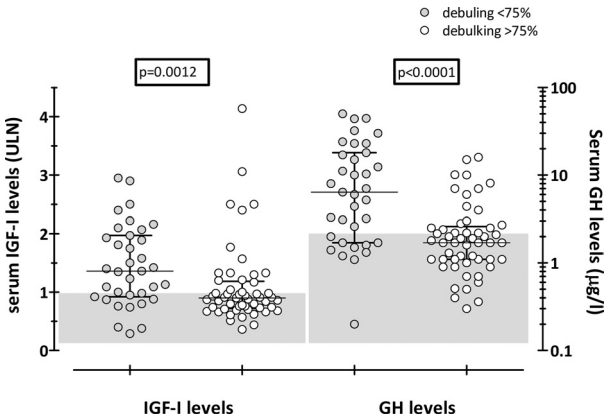

FIG. 5. Serum IGF-I (*left*) and GH levels (*right*) after a second course of SA therapy after surgery in patients shown to be poorly responsive to a presurgical SA course. Data are shown according to the amount of tumor removal on surgery less than or at least 75%. Data are derived from Ref. 174.

1. Surgical debulking

In several independent studies, surgical removal, although partial, has been found to increase the response to subsequent therapy with SA. Particularly, Petrossians *et al.* (173) showed that the gross total tumor resection increases the probability of achieving safe levels of GH and IGF-I by postoperative administration of SA. Similarly, we (174) reported that surgical debulking of a GH-secreting pituitary adenoma increases the success rate in achieving safe levels of IGF-I after treatment with SA without impairing pituitary function (Fig. 5). More recently, Karavitaki *et al.* (127) demonstrated that surgical debulking of pituitary tumors causing acromegaly improved subsequent postoperative control by the SA lanreotide.

2. Radiotherapy and radiosurgery

Radiotherapy, administered as conventional external-beam or as stereotactic radiosurgery with the use of gamma-knife, is reserved for patients with recurred or persisted disease activity after unsuccessful surgery and those who are resistant or intolerant to medical treatment.

Conventional pituitary irradiation (177) has been shown to be effective and safe in reducing both serum GH and IGF-I concentrations in patients with acromegaly showing a poor control after surgery and/or medical therapy with SA. However, the functional decline of other pituitary axes has been described 10 yr after irradiation in more than 40% of patients (177). In hypersecreting tumors (178), stereotactic radiosurgery showed an effective

antisecretory action, inducing disease remission in about 50% of cases, but also a low risk of recurrence (2–10% of cases). The time to remission is estimated to range from 12 to 60 months. Hypopituitarism, the main adverse effect, is observed in 20–40% of cases. When compared with conventional fractionated radiotherapy, radiosurgery revealed a lower rate of remission, counterbalanced by a more rapid efficacy and a lower rate of hypopituitarism. After a 10-yr follow-up, normal IGF-I (179) values have been observed in 82% of patients, whereas no visual impairment, disease recurrence, tumor growth, or secondary cerebral tumor occurred. Half of the patients developed one or more new deficiencies, with clinical or subclinical hypoadrenalism, hypothyroidism, hypogonadism, and GH deficiency being recorded in 40, 11, 13, and 6% of patients, respectively. At the time of gamma-knife radiosurgery, GH value was the best negative predictor of cure, and margin dose was the best positive predictor of new hypopituitarism.

3. High-dose SA treatment

In acromegaly, at least 30% of patients respond inadequately to conventional long-acting SA treatment. In these patients, response to treatment may be improved by increasing SA frequency or dosage. In particular, the dose of octreotide LAR varies among studies, ranging between 10 and 40 mg/month. Two independent studies have investigated the clinical and biochemical improvement in acromegalic patients treated with high-frequency (30 mg every 21 d) or high-dose (40 or 60 mg every 28 d) octreotide LAR (137, 141). In both papers (137, 141), a significant decrease in hormonal levels until IGF-I normalization has been found, so that disease control was described in at least an additional 25% of patients. Moreover, when octreotide LAR was increased to 40 mg/month, the achievement of disease control was associated with a significant tumor shrinkage at end treatment (137). High-dose octreotide LAR treatment did not impair glucose tolerance more than conventional-dose octreotide LAR. Gastrointestinal tolerability did not worsen either during high-frequency or high-dose (137) octreotide LAR therapy.

4. Pegvisomant

Pegvisomant is a new genetically engineered GH analog that acts by binding peripheral GH receptors and so blocking IGF-I synthesis. Therefore, in patients with proven resistance to long-term high-dose SA treatment after unsuccessful surgery and/or radiotherapy, the primary goal of pegvisomant is to reduce serum IGF-I levels to within the age-related reference range, whereas GH levels are not lowered and cannot be used as a disease marker (180). In an 18-month study (181), pegvisomant was used, titrating the dose by 5 mg increments until the normalization of IGF-I or the achievement of the maximum dose of 40 mg/d. Normal IGF-I serum levels were achieved in 97% of patients at 12 months. IGF-I normalization has been demonstrated to significantly improve acromegalic comorbidities in terms of both metabolic (182) and cardiovascular (183) complications. Data from the German Observational Surveillance Acrostudy (184) reported that, among 371 patients receiving pegvisomant as monotherapy, 71.3% achieved and maintained normal IGF-I levels after 24 months at 15 mg/d median dose.

5. Combined therapy: somatostatin analogs and cabergoline

Cabergoline is an ergot-derived DA selective for the dopamine receptor type 2 (D_2), with a longer half-life and improved tolerability compared with other DA such as bromocriptine. Cabergoline is comparatively inexpensive and may still have a role as combination treatment with SA in achieving safe GH/IGF-I levels in patients partially responders or nonresponders to SA. In three independent studies (185–187), the addition of cabergoline to SA has been reported to induce a further reduction in IGF-I levels, ranging from 35–47% when compared with SA monotherapy. IGF-I normalization was found in 33% (185) and 42% (186) of patients using cabergoline at 1.1–2.6 mg/wk mean dose. The efficacy of combined therapy with SA and cabergoline in acromegaly has been found to be independent of prolactin serum levels (186).

6. Combined therapy: somatostatin analogs and pegvisomant

In acromegalic patients, particularly those with tumor residual after unsuccessful surgery and/or radiosurgery, the addition of pegvisomant to SA has been demonstrated to significantly decrease IGF-I levels in the case of inadequate control of acromegaly disease activity. In a randomized, controlled, multicenter study (188), combined treatment with SA plus pegvisomant has been found to be effective in normalizing IGF-I levels, improving symptoms, and reducing soft tissue swelling. Serum IGF-I levels normalized in 73% of patients, whereas no significant change was observed in tumor volume. Combination therapy with long-acting SA and pegvisomant, especially as weekly administration, is safe (189). After a long-term observation, mild and transient increase in liver enzyme levels was recorded in 15% of patients; diabetic subjects particularly seem to be more prone to develop a pathological increase in liver function enzymes.

V. Perspectives

A. Pasireotide

Pasireotide (SOM230) is a new analog under strict investigation to treat patients with acromegaly, Cushing's disease, and neuroendocrine tumors, and it will be available soon. This is a cyclohexapeptide with a high affinity for sst_1, sst_2, sst_3, and sst_5, and with a 30–40 times higher affinity than octreotide for sst_1 and sst_5 and a five times higher affinity for sst_3 (190). SOM230 exhibited an affinity binding profile for human SSTR more similar to native SRIF than to either octreotide or lanreotide (191). In contrast to octreotide, SOM230 exhibits particularly high subnanomolar affinity to sst_5 and an improved metabolic stability (192). Preclinical studies suggest that SOM230 is a promising candidate for clinical applications where octreotide and lanreotide were shown to be weakly active or even ineffective (193–195).

In a single-dose, proof-of-concept study (196), 100 μg octreotide and 100 and 250 μg SOM230 were given sc to 12 patients with active acromegaly. A comparable suppression of GH levels by octreotide and 250 μg SOM230 was observed in eight patients (65 $\pm$ 7 *vs.* 72 $\pm$ 7%, respectively), whereas in three patients, the acute GH-lowering effect of 250 μg SOM230 was significantly superior to that of octreotide (70 $\pm$ 2 *vs.* 17 $\pm$ 15%, respectively) (196). Tolerability for SOM230 has been reported to be good, with some patients showing deterioration in glucose tolerance.

A long-term study in patients with acromegaly treated with the LAR formulation of SOM230 is currently ongoing. A more potent inhibition of IGF-I, with little tachyphylaxis, was similarly observed in studies using a new long-acting-release formulation of SOM230 (197). Results from this study showed that 35 d after a single sc injection of SOM230 long-acting-release (8 mg/kg), IGF-I was still reduced by 49%, whereas the same dose of LAR reduced IGF-I by 9% (197).

B. Dopastatins

In some patients with acromegaly, the combination of SA with DA has been shown to be more effective than treatment with the individual SA (186). Although the mechanisms underlying an additive effect of SA and DA are not clear, under experimental conditions SSTR and D_2 have been shown to heterodimerize in the presence of appropriate ligands and to generate a novel hybrid receptor that more effectively promotes adenylate cyclase inhibition than activation of the individual receptors (198). In cultures of GH-secreting tumor cells, Saveanu *et al.* (199) have previously observed an additive suppression of GH and PRL secretion produced by a chimeric sst_2-D_2 ligand that exceeds the suppression induced by octreotide in the same tumors.

In a phase II exploratory study, the BIM23A760 binding D_2 and sst_5, after a single administration of 1 or 4 mg sc, induced a greater than 30% suppression of GH for 2 d associated with decreased IGF-I and suppressed PRL levels (200).

This new class of chimeric drugs, combining receptor binding activity to somatostatin and dopamine receptors in the same molecule, is under investigation to treat acromegaly and, possibly in the future, other types of pituitary and neuroendocrine tumors.

VI. Summary

SA are a cornerstone of medical therapy in acromegaly, used both as first-line treatment in patients with large macroadenomas or patients with clinical conditions so severe as to prevent unsafe reactions during anesthesia, and as second-line treatment after unsuccessful surgery (176). The response to SA is analyzed by considering both control of GH and IGF-I excess and tumor shrinkage. This latter effect is more evident in the patients treated first-line and bearing macroadenomas. Predictors of response are patients' gender, age, initial GH and IGF-I levels, and tumor mass as well as adequate expression of SSTR, particularly sst_2 and sst_5, the most important subtypes associated with inhibition of hormone secretion and cell proliferation, and those with the highest affinity for octreotide and lanreotide. Conversely, no definitive data are available on the mechanisms responsible for a true resistance to SA because only sporadic cases of SSTR gene mutation or impaired signaling pathways have been described in GH-secreting tumors so far.

More likely, biochemical and tumor responses to SA depend on several factors, including treatment duration and dosage of the drug used, so that a definition of resistance based on short-term treatments using low doses of long-acting SA is deceptive. Current data suggest that response to SA should be analyzed by taking together the effects on GH and IGF-I and those on tumor mass because only the lack of both responses might be considered as a poor response or resistance. This latter evidence seems to occur in 25% of treated patients after 12 months of SA therapy with currently available long-acting SA.

VII. Conclusions

The critical analysis of literature indicates that only a proportion of patients, roughly 25% of all patients receiving SA as the only therapy for at least 12 months, do not have any significant response in terms or GH and/or IGF-I control, show a decrease by at least 20% of initial tumor size, and might be considered resistant or poorly responsive to SA. In these patients, after 12 months of treatment with

SA, treatment alternatives such as GH-receptor antagonist or DA, alone or in combination with SA, surgery, and radiotherapy, might all be used according to individual patient characteristics.

Surgery in particular might be associated with a better response in terms of IGF-I control in the patients previously shown to be poorly responsive to SA if at least 75% of the tumor is removed.

The phenotypes more likely associated with full response to SA are females in the fertile age range or treated with estrogens or elderly patients.

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