EXPERIMENTAL STUDY

Efficacy of chimeric molecules directed towards multiple somatostatin and dopamine receptors on inhibition of GH and prolactin secretion from GH-secreting pituitary adenomas classified as partially responsive to somatostatin analog therapy

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Abstract

Objective: This study compared the potency of a somatostatin receptor (sstr)2–sstr5 analog, BIM-23244, of an sstr2-dopamine D2 receptor (sstr2-DAD2) molecule, BIM-23A387 and of new somatostatin-dopamine chimeric molecules with differing, enhanced affinities for sstr2, sstr5 and DAD2, BIM-23A758, BIM-23A760 and BIM-23A761, to suppress GH and prolactin (PRL) from 18 human GH adenomas that are partially responsive to octreotide or lanreotide.

Materials and methods: The sstr2, sstr5 and DAD2 mRNA levels were determined by RT-PCR. The effect of drugs was tested in cell cultures at various concentrations.

Results: In all tumors, the sstr2, sstr5 and DAD2 mRNA levels were coexpressed (mean levels $\pm$ S.E.M. 0.4 ± 0.1 , 5.3 ± 1.9 and 2.0 ± 0.4 copy/copy β -glucuronidase). In 13 tumors, the maximal suppression of GH secretion produced by BIM-23A387 ($30 \pm 3\%$) and BIM-23244 ($28 \pm 3\%$) was greater than that produced by octreotide ($23 \pm 3\%$). In six out of 13 tumors, BIM-23A758, BIM-23A760 and BIM-23A761 produced greater maximal suppression of GH secretion than octreotide (33 ± 5 , 38 ± 2 and 41 ± 2 vs $24 \pm 2\%$). Their EC₅₀ values were 10, 2 and 4 pmol/l. BIM-23A761 was more effective than BIM-23A387 in GH suppression (41 ± 2 vs $32 \pm 4\%$). The new chimeric molecules produced maximal PRL suppression greater than octreotide (62 ± 8 to 74 ± 5 vs $46 \pm 11\%$).

Conclusions: Novel dopamine-somatostatin chimeric molecules with differing, enhanced activity at sstr2, sstr5 and DAD2, consistently produced significantly greater suppression of GH and PRL than either octreotide or single-receptor-interacting ligands in tumors from patients classified as only partially responsive to octreotide therapy. The higher efficacy of the chimeric compounds was, at least partially, linked to their high affinity for sstr2 (IC₅₀ 1–10 pmol/l). The other mechanisms by which such molecules produce an enhanced inhibition of GH remain to be elucidated.

European Journal of Endocrinology 153 135–141

Introduction

Medical treatment of acromegalic patients using the somatostatin (SST) analogs, octreotide or lanreotide, allows effective control of growth hormone (GH) hypersecretion and restores normal plasma insulin-like growth factor-I (IGF-I) values in about 60% of patients (1). This percentage is likely overestimated as most of the series reported in this meta-analysis selected the patients on the basis of a previous good response to an acute octreotide testing which lowered GH values below 5 μ g/l. Dopamine (DA) agonists also suppress GH hypersecretion in some acromegalic patients (2). The DA superagonist, cabergoline, allows effective

control of GH and IGF-I in 29–39% of patients (3, 4). In some cases, the combination of SST and DA agonists has been shown to be more effective than treatment with the individual SST agonists (5). While the mechanisms underlying an additive effect of SST and DA analogs are not clear, SST receptors (sstr) and DA D2 receptors (DAD2) have been demonstrated under experimental conditions to heterodimerize in the presence of appropriate ligands, and to generate a novel hybrid receptor that more effectively promotes adenylylate cyclase inhibition than activation of the individual receptors (6). In cultures of GH-secreting tumor cells, we have previously observed an additive suppression of GH and PRL secretion produced either by a bispecific

sstr2-sstr5 ligand (7) or by a chimeric sstr2 + DAD2 ligand (8) that exceeds the suppression induced by octreotide in the same tumors.

The initial aim of the present study was to compare the efficacy of the sstr2-sstr5 bispecific SST analog, BIM-23244, and the sstr2-DAD2 chimeric molecule, BIM-23A387, in suppressing GH and PRL in 18 consecutive GH-secreting tumors collected from acromegalic patients previously classified as only partially responsive to long-term octreotide or lanreotide treatment. As the data obtained from this part of the study showed that most of the tumors that are partially responsive to octreotide responded to both dual receptor ligands, a new class of chimeric molecules with differing, enhanced affinities for sstr2, sstr5 and DAD2, was developed and tested in a subset of the GH-secreting tumors from patients partially responsive to octreotide. This latter study demonstrated that the new chimeric molecules with enhanced activity have the greatest efficacy in suppressing both GH and PRL.

Patients and methods

Patients

Eighteen acromegalic patients were enrolled in this study which was approved by the Ethics Committee of the University of Aix-Marseille II. They were 15 women and three men aged 37 ± 3 years (mean $\pm$ S.E.M.). Initially, all the patients presented with invasive macroadenomas and were first treated with either sandostatin LAR (20–30 mg i.m., monthly) or with somatuline SR (90–120 mg i.m., monthly), for 626 months before surgery. In eight patients, the DA agonist, cabergoline, was added to the SST analog treatment (1.5–3.5 mg per os, weekly). In this series, the mean initial GH plasma value measured before any treatment ($82 \pm 44 \mu\text{g/l}$) was only partially lowered by such long-term medical treatments ($37 \pm 6 \mu\text{g/l}$). In none of

the cases did the depot preparations of octreotide or of lanreotide, even with the addition of the DA agonist, cabergoline, normalize either plasma GH or IGF-I values. These treatments were withdrawn at least 1 month before transphenoidal surgery in all patients. After surgery, a portion of each tumor tissue was analyzed for quantitative expression of sstr2, sstr5 and DAD2 mRNAs. The remainder of each tissue was dispersed for cell culture studies.

Hormone assays

GH and PRL were measured using commercial immunoradiometric kits (Immunotech, Marseilles, France). Normal GH values ranged from 0.2 to $2.4 \mu\text{g/l}$, normal PRL values ranged from 1 to $24 \mu\text{g/l}$ in women and from 1 to $17 \mu\text{g/l}$ in men. After an ethanol–acid extraction, the plasma IGF-I assay was performed using the IGF-I RIA kit from Nichols Institute Diagnostics (San Juan Capistrano, CA, USA). The normal ranges, according to sex and age, were established by our laboratory.

Compounds

The BIM compounds were produced and provided by IPSEN (Milford, MA, USA). Their affinities for the different human receptors were calculated from saturation binding assays performed on membrane preparations from transfected CHO-K1 cells expressing the different sstr or DAD2 subtypes, according to a previously published method (9). The individual characteristics of these compounds are listed in Table 1. Octreotide was supplied by Novartis Pharmaceuticals (Basel, Switzerland). The SST analogs were dissolved in 0.01 mol/l acetic acid containing 0.1% purified human serum albumin (Life Technologies Inc., Cergy-Pontoise, France). The DA compounds were initially prepared as 10^{-3} mol/l solutions in 0.01 mol/l acetic acid and

Table 1 Human sstr and DAD2 binding affinities of the various DA and SST analogs. Data are from radioligand assays using membranes from transfected CHO-K1 cells expressing the human DAD2 or the human sstr subtypes. Values are from IPSEN (J E Taylor & M D Culler).

Compound	sstr1	sstr2	sstr3	sstr4	sstr5	DAD2
SST 14	2.3	0.2	1.4	1.8	1.4	ND
Octreotide	1140	0.6	34	7030	7.0	ND
BIM-23197	6016	0.2	27	897	9.8	> 1000
BIM-23268	12	28	5.5	36	0.4	ND
BIM-53097	> 1000	> 1000	> 1000	> 1000	> 1000	22
BIM-23244	> 1000	0.3	133	> 1000	0.7	ND
BIM-23A387	293	0.2	77	> 1000	26	22
BIM-23A758	468	0.1	324	> 1000	27	13
BIM-23A760	622	0.03	160	> 1000	42	15
BIM-23A761	462	0.06	52	> 1000	3.7	27
BIM-23A765	> 1000	0.2	76	> 1000	7	9

ND, not done.

70% ethanol. All drugs were stored at -80°C as 10^{-3} mol/l solutions. For each experiment, working solutions were made by diluting a fresh aliquot with culture medium.

Detection of *sstr* and *DAD2* mRNAs

Total RNA was extracted from 30–60 mg tissue from each tumor using the RNeasy isolation system (Qiagen, Courtaboeuf, France). One microgram of total RNA prepared from tumoral pituitary tissues was used for cDNA synthesis, as previously described (8). To quantify *sstr* and *DAD2* mRNAs, a quantitative PCR was performed by TaqMan Gold nuclease assay (Perkin Elmer, Foster City, CA, USA) and the ABI PRISM 7700 sequence Detection System (Perkin Elmer) for real-time amplifications, according to the manufacturer's protocol. The *sstr* and *DAD2* mRNA levels were normalized to the β -glucuronidase (β -Gus) mRNA levels obtained in the same reaction, as previously described (8). For each measurement, three independent RT-PCR analyses were performed.

Cell culture studies

A portion of each tumor obtained at surgery was dissociated by enzymatic and mechanical methods. Depending on the tumor, $7\text{--}50 \times 10^6$ isolated cells were obtained. These cells were plated in multiwell culture dishes (Costar 3524; Costar, Brumath, France) which were coated with extracellular matrix from bovine endothelial corneal cells, as previously described (10), at a density of 2×10^4 cells per well in Dulbecco's minimum Eagles' medium supplemented with 1% fetal calf serum, antibiotics, insulin, transferrin and selenium. The pharmacological studies were performed between days 4 and 8 of culture. Octreotide, the biselective *sstr2-sstr5* SST analog, BIM-23244, and the SST-DA chimeric molecule, BIM-23A387, were tested at concentrations ranging from -13 to -8 mol/l in order to examine the dose–response relationship and to determine the EC_{50} for GH inhibition. In six of these tumor cell cultures, we compared the dose–response inhibition of GH secretion (and PRL in four GH-PRL tumors) achieved by the four new chimeric molecules with differing, enhanced affinity for *sstr2*, *sstr5* and *DAD2* subtypes. In the same experiments, we also directly compared the dose–responses for GH achieved by octreotide and the original SST-DA chimeric molecule, BIM-23A387.

Statistics

The results are presented as the means $\pm$ S.E.M. Statistical significance between two unpaired groups was determined by the Mann–Whitney test. To measure the strength of association between the pairs of variables without specifying dependencies, Spearman

order correlations were used. $P < 0.05$ was considered significant for all tests.

Results

DAD2 and *sstr* subtype mRNA expression

Real-time PCR quantitative analysis was performed on 15 out of 18 tumor fragments. The mean *sstr2*, *sstr5* and *DAD2* mRNA levels were 0.4 ± 0.1 , 5.3 ± 1.9 and 2.0 ± 0.4 copy/copy β -Gus respectively. The mean *sstr2*, *sstr5* and *DAD2* mRNA levels were also measured in nine other GH-secreting adenomas from patients classified as sensitive to octreotide, as they had achieved normal GH and IGF-I values under octreotide or lanreotide. These values were 1.7 ± 0.3 , 4.8 ± 0.7 and 4.0 ± 0.5 copy/copy β -Gus respectively. The mean *sstr2* mRNA level in tumors from patients partially responsive to octreotide was markedly lower than that from octreotide-sensitive patients ($P < 0.001$). *Sstr5* and *DAD2* mRNA were well expressed in all tumors from patients partially responsive to octreotide and did not differ statistically from the level observed in tumors from octreotide-sensitive patients. No correlation between the response to treatment and the level of *sstr5* or *DAD2* expression could be established.

Maximal GH suppression by octreotide, SST and DA analogs

The effect of octreotide and selective SST and DA analogs on GH secretion in cultured cells derived from the 18 tumors was measured after a 12-h incubation period. The maximal inhibition of GH release induced by 1 or 10 nmol/l octreotide, as compared with controls (medium alone), was only partial and ranged from 6 to 35% according to the individual tumor (mean GH suppression by octreotide $23 \pm 3\%$). When the 18 cell cultures were treated with the *sstr2*-selective analog, BIM-23197, the *sstr5*-selective analog, BIM-23268 or the *DAD2* compound, BIM-53097, a mean maximal inhibition of GH release of 24 ± 3 , 20 ± 3 and $20 \pm 3\%$ respectively was obtained. Of the three compounds, BIM-23197 produced the greatest maximal GH suppression in the majority (12 out of 18) of cases. However, the greatest absolute maximal GH suppression was obtained with the *DAD2* analog, BIM-53097, in four tumors and with the *sstr5*-preferring compound, BIM-23268, in two cases.

Dose-related GH suppression with octreotide, the biselective *sstr2-sstr5* analog, BIM-23244, and the chimeric *sstr2-DAD2* analog, BIM-23A387

In the 18 octreotide partially responsive tumors, octreotide, BIM-23244 and BIM-23A387 were tested at various concentrations to determine their respective

Figure 1 Mean dose-related GH suppression in cell cultures from 18 adenomas collected from acromegalic patients classified as partially responsive to octreotide. (Left panel) Dose-related GH suppression obtained in 15 tumors (group 1) with greater GH suppression with BIM-23244 and BIM-23A387 than with octreotide. (Right panel) Dose-related GH suppression obtained in five tumors (group 2) equally responsive to BIM-23244, BIM-23A387 and octreotide. Results are expressed as mean $\pm$ S.E.M. percent GH suppression vs control (C=medium alone). Each point represents the mean of four replicate wells.

potencies in suppressing GH secretion. Two individual patterns of dose-related inhibition of GH release were identified, as shown in Fig. 1. In the first group, consisting of 13 out of 18 tumors, the biselective molecules, BIM-23244 and BIM-23A387, at nanomolar concentrations, produced maximal mean GH suppression of 28 ± 3 and $30 \pm 3\%$ respectively, greater by 23–43% than that obtained with octreotide ($21 \pm 2\%$; $P < 0.04$ and $P < 0.01$ for BIM-23244 and BIM-23A387 vs octreotide). The EC_{50} values for octreotide, BIM-23244 and BIM-23A387 were 150 pmol/l (range 6–250), 10 pmol/l (range 2–100) and 1 pmol/l (range 0.5–50) respectively. The comparison between the hybrid molecules showed a significantly ($P < 0.05$) better GH suppressive effect with BIM-23A387. The second group consisted of five tumors that displayed similar dose–response curves for GH suppression with octreotide, BIM-23244 and BIM-23A387. The differences between the EC_{50} values for octreotide, BIM-23244 and BIM-23A387 (8020 pmol/l) did not reach statistical significance.

Effects of new chimeric molecules with differing, enhanced affinities for sstr2, sstr5 and DAD2 on GH suppression

Cell cultures from six tumors from the first group that displayed enhanced inhibition of GH release with the sstr2-DAD2 compound, BIM-23A387, were used to test a series of four new chimeric molecules with differing, enhanced affinities for sstr2, sstr5 and DAD2 in order to find out if altering the activity ratio of these

Figure 2 Mean dose-related GH suppression obtained with the trihybrid compounds, BIM-23A758, BIM-23A760, BIM-23A761 and BIM-23A765, in cell cultures from six adenomas that were partial responders to octreotide. (Left panel) Mean dose-related GH suppression with octreotide and BIM-23A387. (Right panel) Mean dose-related GH suppression obtained with four new chimeric molecules (BIM-23A758, BIM-23A760, BIM-23A761 and BIM-23A765). Results are expressed as mean $\pm$ S.E.M. percent GH suppression vs control (C=medium alone). Each point represents the mean of four wells.

three receptors could produce a higher suppression of GH secretion than the activation produced by the original sstr2-DAD2 compound, BIM-23A387. As shown in Fig. 2, the mean maximal GH suppression achieved with the new chimeric compounds, BIM-23A758, BIM-23A760, BIM-23A761 and BIM-23A765, varied between 24 ± 1 and $41 \pm 2\%$. The mean maximal GH suppression obtained with BIM-23A765 was similar to that obtained in the same tumors with octreotide ($26 \pm 2\%$). The mean maximal GH suppression obtained with the three other new chimeric compounds was significantly greater than that obtained with octreotide (33 ± 5 , 37 ± 1 and $41 \pm 2\%$ with BIM-23A758, BIM-23A760 and BIM-23A761; $P < 0.05$, $P < 0.03$, and $P < 0.03$ respectively vs octreotide). The EC_{50} values for these three compounds ranged from 2 to 10 pmol/l.

In these tumor cell cultures, the dose-related inhibition of GH secretion was also compared with that obtained with the original sstr2-DAD2 compound, BIM-23A387. As shown in Fig. 2, a mean suppression of GH release of $41 \pm 2\%$ was obtained with BIM-23A761 vs $32 \pm 4\%$ for BIM-23A387 ($P < 0.05$) and $26 \pm 2\%$ for octreotide ($P < 0.01$).

BIM-23A761 vs the combination of sstr2, sstr5 and DAD2 monospecific drugs

In one tumor cell culture, the GH suppressive effect of the chimeric compound, BIM-23A761, was compared with an equimolar combination of the monospecific sstr2-, sstr5- and DAD2-preferential compounds. As shown in Fig. 3, the mean dose-related pattern of GH suppression produced by BIM-23A761 was markedly distinct from that induced by the combination of BIM-23197 + BIM-23268 + BIM-53097 with a mean maximal GH suppression of 49 ± 3 and $38 \pm 2\%$

Figure 3 Mean dose-related GH suppression with BIM-23A761, the combination of BIM-23197 + BIM-23268 + BIM-53097 and octreotide in one adenoma that was partially responsive to octreotide. Results are expressed as the mean of four wells $\pm$ S.E.M. percent GH suppression vs control (C = medium alone). Each point represents the mean of four wells.

respectively ($P < 0.03$). Again the superior suppression of GH secretion by the chimeric molecule, as compared with octreotide (maximal suppression $22 \pm 2\%$), was highly significant ($P < 0.01$).

Effects of the DA-SST chimeric compounds on PRL release

Dose-related inhibition of PRL secretion by the trihybrid compounds, BIM-23A758, BIM-23A760, BIM-23A761 and BIM-23A765, was analyzed in cell cultures of four different GH + PRL-secreting tumors. As shown in Fig. 4, all the compounds were highly effective in suppressing PRL secretion (mean EC_{50} values = $2\text{--}10$ pmol/l; maximal suppression 68 ± 10 to $74 \pm 4\%$, depending on the compound). In comparison, octreotide and the original, chimeric compound, BIM-23A387, produced only 45 ± 11 and $54 \pm 8\%$

Figure 4 Mean dose-related PRL suppression obtained with the trihybrid compounds, BIM-23A758, BIM-23A760, BIM-23A761 and BIM-23A765, in cell cultures from four mixed GH-PRL adenomas. (Left panel) Dose-response GH suppression by octreotide and BIM-23A387. (Right panel) Dose-response GH suppression by the four new, multi-receptor-interacting chimeras. Results are expressed as mean $\pm$ S.E.M. percent PRL suppression vs control (C = medium alone). Each point represents the mean of four replicate wells.

maximal inhibition of PRL secretion, with EC_{50} values of 200 and 5 pmol/l respectively.

Discussion

Acromegalic patients classified as only partially responsive to long-term therapy with octreotide or lanreotide represent 40–50% of the total patient population (1). They are defined by a failure to achieve normalization of GH and IGF-I plasma levels despite at least 3–6 months of treatment with high doses of octreotide or lanreotide. Such a partial response is a primary phenomenon not linked to tachyphylaxis, as observed with other neuroendocrine tumors (11). It appears to be linked to a selective loss of sstr2 expression (12, 13). The analysis of sstr2, sstr5 and DAD2 mRNA profiles in the present series of tumors confirms such a selective loss of sstr2. In recent years, the additive effect of combined sstr2 and sstr5 preferential compounds on GH suppression, in tumors partially responsive to octreotide, has been demonstrated in cell culture studies (7, 13, 14). This finding led to the introduction of the sstr2-sstr5 dihybrid compound, BIM-23244 (7, 15). The improved GH-suppressive effect was interpreted as a rescue of response acting through the highly expressed sstr5 in tumors expressing low levels of sstr2 (7). The present data confirmed, in about 72% of GH-secreting tumors, a lower EC_{50} and a higher maximal GH suppression for BIM-23244 as compared with octreotide. The reasons why some octreotide-resistant tumors do not display enhanced sensitivity to the bispecific molecule are presently unknown. Recently, another new SST analog that interacts with sstr1, sstr2, sstr3, but mainly with sstr5 (IC_{50} for sstr5 0.16 nmol/l), SOM230, has also been reported to exhibit enhanced potency in suppressing GH and PRL secretion from some GH-secreting tumors that are partial responders to octreotide, both *in vitro* and *in vivo* (13, 16). Taken together, these studies indicate that new somatostatinergic drugs directed towards different sstrs can achieve a better GH suppression than octreotide in some acromegalic tumors.

DA agonists were the first drugs used in the medical treatment of acromegaly. The efficacy of dopaminergic treatment increased to reach 29–39% of patients with the advent of the high affinity D2 analog, cabergoline (3, 4). Until recently, it was believed that only GH-PRL mixed tumors could be controlled by cabergoline; however, a recent study demonstrated that the efficacy of adding cabergoline treatment in 42% of patients partially responsive to octreotide or lanreotide therapy was independent of PRL status (5). In our study, as in previous studies (8, 17), the chimeric molecule, BIM-23A387, displayed enhanced potency in suppressing GH secretion in the 13 out of 18 cell culture studies. In another study, using the antagonists sulpiride and BIM-23454, which antagonize DAD2 and sstr2

respectively, the higher efficacy of BIM-23A387 was attributed in large part to its dopaminergic pharmacophore site (17). We have previously demonstrated that both antagonists were able to partially reverse the activity of BIM-23A387 (8). Such apparently contradictory results can be explained by the different conditions used in the two studies. Because the sstr2 antagonist, BIM-23454 (18), has a low affinity for sstr2 (IC_{50} 32 nmol/l) as compared with that of BIM-23A387 (IC_{50} 0.16 nmol/l), it can reverse the action of BIM-23A387 when BIM-23A387 is used at picomolar concentrations (8) and not at a higher concentration of 4 nmol/l (17). Finally, when the dose-related inhibition of GH secretion attained with BIM-23A387 and with BIM-23244 were compared, BIM-23A387 displayed an EC_{50} ten times lower than that of BIM-23244.

The second part of our study explored the possibility of a further enhancement of GH suppression from GH-secreting tumors partially responsive to octreotide by using new chimeric molecules that have differing, enhanced activities at sstr2, sstr5 and DAD2. From 12 different compounds, four such chimeric molecules with variable affinities for each receptor were selected. All four of these compounds displayed an exceptionally high affinity for sstr2 (IC_{50} 10–100 pmol/l). In the tumors treated with these compounds, in cell culture, GH secretion was suppressed with an EC_{50} significantly lower than that achieved with octreotide (1–10 vs 80 pmol/l). Three of the four new chimeric molecules also induced maximal GH suppression that was significantly greater than that produced by octreotide. Finally, the most potent sstr2-interacting chimeric molecules produced the greatest maximal GH inhibition. An increase in sstr2-binding affinity has previously been achieved with a non-peptide selective agonist, L-054522, which binds to the human sstr2 with a reported K_i of 0.01 nmol/l (19). High binding affinity for sstr2 is apparently a key point in the higher efficacy of the chimeric compounds; however, it does not completely explain the greater GH-suppressing efficacy of the new chimeric compounds since, among our compounds, BIM-23A765, despite its high affinity for sstr2, did not suppress GH secretion more efficiently than octreotide. It has been hypothesized that such multiple ligands could induce receptor homo- and hetero-dimerization as experimentally demonstrated in transfected cell lines (6, 20–22). The first evidence that such a heterodimerization process may occur in normal cells was presented in a study using fluorescence resonance energy transfer (FRET) in cortical neurons in culture (23). Another explanation for the greater efficacy of the multi-receptor-interacting chimeric compounds could be due to a different interaction between the ligand and its receptor that allows prolonged stabilization of its active conformation or alternation of the rate of internalization (24–26). Accordingly, a β -arrestin-dependent recycling of the sstr2 to the plasma membrane that may prevent sstr2

but not sstr5 degradation has recently been described using sstr2-transfected HEK293 cells (27). One final explanation for the greater potency of the multi-receptor-interacting chimeric molecules may simply be due to the fact that they can bind and activate multiple receptors. This ability increases the chance that once the ligand is released from one receptor it will rapidly occupy another receptor. Presently, there is no firm explanation for the unique activities of these novel chimeric compounds, and additional studies, such as those using fluorescent SST analogs or FRET, as recently studied in live adrenocorticotropin-secreting AtT20 cells (28), are needed to explain the enhanced efficiency of these ligands.

In conclusion, our present study extends the notion that ligands directed towards both DA and SST receptors can achieve greater hormone (GH and PRL) suppression than that achieved by octreotide in human GH-secreting adenomas. These new chimeric molecules may represent a new concept in drug design allowing greater efficacy in the treatment of a wider range of acromegalic patients. Indeed, clinical studies are needed in order to evaluate the tolerance of such compounds.

Acknowledgements

The skillful help of Mrs C Taverna in the editing of the manuscript was greatly appreciated. We are grateful to Mrs S Guillen for technical help. This work was supported by a grant from Biomeasure, Inc. (Milford, MA, USA) and by the Association pour le Développement et la Recherche Médicale (Marseille, France).

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Received 10 March 2005

Accepted 13 April 2005