A Single-Dose Comparison of the Acute Effects between the New Somatostatin Analog SOM230 and Octreotide in Acromegalic Patients

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Treatment with the somatostatin receptor (sst) subtype 2 predominant analogs octreotide and lanreotide induces clinical and biochemical cure in approximately 65% of acromegalic patients. GH-secreting pituitary adenomas, which are not controlled, also express sst5. We compared the acute effects of octreotide and SOM230, a new somatostatin analog with high affinity for sst2, sst3, and sst5 on hormone release in acromegalic patients. In a single-dose, proof-of-concept study, 100 μg octreotide and 100 and 250 μg SOM230 were given sc to 12 patients with active acromegaly. Doses of 100 and 250 μg SOM230 dose-dependently suppressed GH levels from 2–8 h after administration (−38 ± 7.7% vs. −61 ± 6.7%, respectively; P < 0.01). A comparable suppression of GH levels by octreotide and 250 μg SOM230 was observed in eight patients (−65 ± 7% vs. −72 ± 7%, respectively). In three patients, the acute GH-lowering effect of 250 μg SOM230 was significantly superior to that of octreotide (−70 ± 2% vs. −17 ± 15%, respectively; P < 0.01). In one patient, the GH-lowering effect of octreotide was better than that of SOM230. Tolerability for SOM230 was good. Glucose levels were initially slightly elevated after octreotide and SOM230, compared with control day, whereas insulin levels were only significantly suppressed by octreotide. We conclude that SOM230 is an effective GH-lowering drug in acromegalic patients with the potential to increase the number of patients controlled during long-term medical treatment. (J Clin Endocrinol Metab 89: 638–645, 2004)

In the majority of patients, acromegaly is caused by a GH-secreting pituitary adenoma, resulting in high circulating GH and IGF-1 concentrations. The first choice of medical treatment are the somatostatin (SS) analogs, a safe and effective strategy, mimicking the action of the native peptide SS in its inhibitory effect on GH release by the adenoma cells (1). The first clinically available SS analog octreotide (OCT) has been shown to be effective as primary or secondary therapy for acromegalic patients (2–5). Several studies have demonstrated that long-term therapy with OCT or lanreotide, administered either sc or as a long-acting depot preparation by im injection, induced clinical and biochemical cure in approximately 65% of patients (6–10). Still, a significant percentage of GH-secreting pituitary tumors seems relatively resistant to OCT and lanreotide, and this may be explained in part by a variable tumoral expression or reduced receptor density of the five known SS receptor (sst) subtypes on the adenomas of these patients (11). Functional evidence for the existence of sst subtypes comes from studies using human fetal pituitary cell cultures in which SS regulates GH and TSH secretion mainly by sst2 and sst5 and prolactin (PRL) secretion mainly by sst5 (12). Most GH-secretting pituitary adenomas predominantly express mRNA for sst2 and sst5, whereas sst1 and sst3 are moderately expressed and sst1 not found (13, 14). SS binds with high affinity to all five sst subtypes, whereas OCT and lanreotide display a high, low, and moderate affinity to sst2, sst1–4, and sst1–5, respectively. Saveanu et al. (15) compared the in vivo sensitivity of GH release for OCT in nine acromegalic patients with the tumor mRNA expression for sst2 and sst5 subtypes. It was observed that sst2 mRNA expression was lower, and sst5 mRNA was higher in adenomas that were partially sensitive to OCT, compared with OCT-sensitive adenomas. In the group of partially OCT-sensitive tumors, both the sst5-preferential analog BIM23268 and especially the sst2 and sst5 bispecific compound BIM23244, were quite effective in suppressing GH secretion. These data indicate that due to the heterogeneous expression of sst2 and sst5 subtypes in GH-secreting adenomas, a bispecific analog, such as BIM-23244 that can activate both receptors, may achieve a better control of GH hypersecretion of GH-producing pituitary tumors than OCT.

Bruns et al. (16) and Lewis et al. (17) synthesized SOM230, a stable SS analog with a more universal binding profile to sst subtypes. By using alanine scanning technology, essential functional groups of the SS peptide responsible for the high affinity to all five sst subtypes were detected. Incorporation of four synthetic amino acids and two essential amino acids of SS into a stable cyclohexapeptide template resulted in SOM230, a compound that binds with a high affinity to sst1, sst2, sst3, and sst5 and with low affinity to sst4. In rats, dogs,
and monkeys, SOM230 potently and dose-dependently decreases GH and IGF-I levels. Only minimal desensitization of the suppressing effect of SOM230 on IGF-I levels under physiological conditions was observed, which is in contrast to what has been seen in rodents with the effect of OCT. Additional characteristics of SOM230 include a favorable terminal elimination half-life of 27 h in humans as well as the preliminary evidence that glucose levels in rats and dogs remain normal during long-term administration of the compound.

Here, we present the detailed analysis of the first single-dose, proof-of-concept study with SOM230 in acromegalic patients. A double-blind, randomized, crossover study was performed to compare the in vivo effects of a single dose of SOM230 to OCT on GH release, to assess its safety and tolerability in 12 patients with active acromegaly.

**Patients and Methods**

Twelve patients with active acromegaly were recruited at the Erasmus Medical Center in Rotterdam, The Netherlands. All subjects had biochemically active disease, with a mean serum GH concentration greater than 5 μg/liter during a 5-h profile and elevated circulating IGF-I levels (age and sex adjusted). GH concentration failed to suppress less than 1 μg/liter after a 2-h 75-g oral glucose tolerance test (oGTT). Table 1 shows the biochemical characteristics of the 12 patients. One insulin-treated patient with type 2 diabetes did not undergo an oGTT. Seven patients had been treated before (see below). In those patients who have been medically treated previously, a washout period after the last dose of medication had to be at least 1 month, 1 wk, 4 months, and 1 month for dopamine agonists, sc formulations of OCT, depot formulations of long-acting somatostatin analogs, and GH receptor antagonists, respectively. One patient had been previously treated by surgery, medical treatment, and irradiation. One patient was treated only with surgery. Two patients had only been medically treated, and three patients were treated with surgery and medical treatment. Five patients were newly diagnosed. Patients with compression of the optic chiasm causing any visual field defect or those requiring surgical intervention for relief of any sign or symptom possibly associated with tumor compression were excluded. The study was approved by the local ethical committee of the Erasmus Medical Center, and all patients gave written informed consent.

**Treatment protocol**

Patients were hospitalized on the control day (CD) for 24 h for the assessment of baseline efficacy parameters. On study d 1, 8, and 15, each patient received at 0900 h a single sc injection of 100 μg OCT, 100 μg SOM230, or 250 μg SOM230 in a randomized, double-blinded, crossover fashion with a minimum 6 d of washout between drug treatments. All patients received standardized meals, served at 0830, 1230, and 1730 h. Blood samples, withdrawn through an indwelling venous catheter placed in the forearm, for the assessment of GH and PRL concentrations, were collected at 30 min, 1 min before, and every hour for 24 h after drug administration. This procedure was repeated on all study days. Furthermore, blood samples for glucose and insulin assessments were collected 30 min, 1 min before, and every half-hour for 2 h after lunch. Blood specimens were centrifuged, and the plasma was frozen at −20 C until it was assayed.

Safety assessments included vital signs (pulse rate, blood pressure, and temperature); electrocardiograms; biochemistry; hematology; and urinalysis.

**Assays**

GH (micrograms/liter), PRL (micrograms/liter), and insulin (milli-units/liter; 1 mU/liter = 7.175 pmol/liter) levels were determined by use of a nonisotopic, automatic chemiluminescence immunoassay system (Immulite; Diagnostic Products Corp., Los Angeles, CA). The intra- and interassay coefficients of variation for GH, PRL, and insulin were 6.0, 5.7, 4.4, and 6.2, 6.4, 5.9%, respectively. Glucose (millimoles/liter; 1 mmol/liter = 18.015 mg/dl) was measured with an automatic hexokinase method (Roche, Almere, The Netherlands). Serum IGF-I (micrograms/liter) was determined with a commercially available nonextraction immunoradiometric assay (Diagnostic Systems Laboratories, Inc., Webster, TX) (intra- and interassay coefficients of variation, 3.9 and 4.2%, respectively).

**In vitro studies**

Two patients underwent transphenoidal surgery 3 months before they entered the study. Adenomatous tissue was collected during operation, and, subsequently, pituitary adenoma cells were isolated as described previously (18). The viability of the resulting cell suspension, as determined by trypan blue dye exclusion, was greater than 95%. The media and supplements were obtained from Life Technologies, Inc. Media and supplements were obtained from Life Technologies, Inc. Bio-Cult Europe (Invitrogen). The cells were allowed to attach for at least 3 d before a 72-h incubation with SS (Sigma, St. Louis, MO), OCT, or SOM230 (both donated by Novartis, Basel, Switzerland) in 1 ml in multwell plates (Corning Costar, Cambridge, MA). The culture medium was Eagle’s MEM with Earle’s salts supplemented with a 1-fold excess of nonessential amino acids, 1 mm sodium pyruvate, 2 mm L-glutamine, 100 μU/ml penicillin, 100 μg/ml streptomycin, and 0.25 μg/ml fungizone, and 10% fetal calf serum (Invitrogen, Breda, The Netherlands). The viability of the resulting cell suspension, as determined by trypan blue dye exclusion, was greater than 95%. The cells were cultured at a density of 0.5–1 × 10⁶ cells/dish/1 ml in multwell plates (Corning Costar, Cambridge, MA). The culture medium was Eagle’s MEM with Earle’s salts supplemented with a 1-fold excess of nonessential amino acids, 1 mm sodium pyruvate, 2 mm L-glutamine, 100 μU/ml penicillin, 100 μg/ml streptomycin, and 0.25 μg/ml fungizone, and 10% fetal calf serum (Invitrogen, Breda, The Netherlands). The viability of the resulting cell suspension, as determined by trypan blue dye exclusion, was greater than 95%.

**TABLE 1. Patients’ characteristics on study entry**

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<th>Patient</th>
<th>Sex</th>
<th>Age (yr)</th>
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<th>PRL (μg/liter)</th>
<th>IGF-I (μg/liter)</th>
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*F, Female; M, male; ND, not determined.

a Mean fasting GH and PRL values, collected in a 5-h time period. Normal values: GH, <5 μg/liter; PRL, <25 μg/liter (men) or <44 μg/liter (women).


c Serum GH level after a 2-h 75-g OGTT (normal nadir GH, <1 μg/liter after 2 h).
Quantitative RT-PCR

Quantitative RT-PCR was performed as described previously (19). Briefly, poly A+ mRNA was isolated during Dynabeads Oligo (dT)30 (Dynal AS, Oslo, Norway) from adenoma cell pellets containing 0.5–1 × 10⁶ cells/sample. cDNA was synthesized using the poly A+ mRNA captured on the Dynabeads Oligo (dT)30 as a solid-phase and first primer. To quantify sst2 and sst5 mRNAs, a quantitative RT-PCR was performed by TaqMan Gold nuclease assay (Perkin-Elmer Corp., Foster City, CA) and the ABI PRISM 7700 sequence detection system (Perkin-Elmer Corp.) for real-time amplification, according to the manufacturer’s instructions. The specific primer sequences (Biosource, Nivelles, Belgium) that were used include: sst2 forward, 5′-TCCGCTCAAGTG-GAGGAGAC-3′; sst2 reverse, 5′-CATCCTCTCCTACGCCAACAG-3′; sst2 reverse, 5′-GGAAGCTCTGCGGGAAGT-3′; hypoxanthine-guanine phosphoribosyl transferase (HPRT, as a control) forward, 5′-TCTGGCTTCTGTCAGGCCAGAT-3′; HPRT reverse, 5′-TCAATCACAAGGCTG-GCTTATATC-3′; /H11032.../H11032; HPRT, 5′-FAM-CCGGACGGCCAAGATGATCACC-TAMRA-3′. The amount of sst2 and sst5 mRNA was determined by means of a standard curve generated in each experiment from known amounts of human genomic DNA. For the determination of the amount of HPRT mRNA, a standard curve was obtained by including dilutions of a pool cDNA known to contain HPRT. The amount of sst2 and sst5 mRNA was calculated relative to the amount of HPRT and is given in arbitrary units.

Statistical analysis

The assumption of normality of all in vitro data was investigated by use of a Kolmogorov-Smirnov test, in which the null hypothesis that the data represented a random sample from the normal distribution was tested. When this hypothesis was not rejected, a paired Student’s t test was used for assessing the statistical significance, compared with the CD. The Wilcoxon’s signed rank test, a nonparametric analog to the paired t test, was used when data did not represent a random sample from normal distribution. Correlation analysis was performed by the use of Spearman’s rank correlation test. In the in vitro studies, one-way ANOVA was used. When significant overall effects were obtained by this method, comparisons were made using Newman-Keuls multiple comparison test. Data are expressed as mean ± SEM. P < 0.05 was considered significant.

Results

Safety and tolerability

Tolerability of OCT and SOM230 was good. Local reactions at the injection site were not observed. Side effects probably related to the study drug were reported in three different patients and were mild (one case of palpitation and sweating after 100 µg SOM230, one case of abdominal discomfort after 100 µg OCT and after 250 µg SOM230). No clinically relevant changes in vital signs, routine chemistry, and urinalysis were observed. Electrocardiogram analyses showed no newly occurring or worsening of known cardiac abnormalities 2 and 24 h after injection with OCT or SOM230.

In vivo studies

Figure 1 depicts the mean circulating 24-h GH concentrations after a single sc injection of 100 µg OCT, 100 µg SOM230, and 250 µg SOM230, compared with CD, for all acromegalic patients investigated. Because all three treatment options appeared to induce their effect on GH secretion predominantly immediately after sc injection, efficacy analysis of OCT and the two dosages of SOM230 was assessed by analysis of the mean GH suppression between 2 and 8 h after sc injection, compared with the same period on the CD. The mean GH levels from 2–8 h after 250 µg SOM230, 100 µg SOM230, and OCT were suppressed by 61 ± 6.7% (P < 0.0001), 38 ± 7.7% (P < 0.001), and 59 ± 9.2% (P < 0.0001), respectively. Furthermore, the 250-µg dosage of SOM230 induced a significantly greater suppressive effect on circulating GH concentrations than the 100-µg dosage of SOM230 (P < 0.01). The inhibitory effect of OCT on GH levels did not differ from SOM230 250 µg (P = not significant), whereas, compared with 100 µg SOM230, a stronger suppression of GH concentrations by OCT was found, although this difference failed to reach statistical significance (P = 0.13).

Analysis of the 12 individual 24-h GH profiles on CD and after administration of the study drugs, revealed three different patterns of response. As illustrated by the 24-h GH profile of patient 6 (Fig. 2A), both OCT and 250 µg SOM230 induced a similar inhibitory effect on circulating GH concentrations [–63%, plasma GH levels 18.9 ± 1.1 µg/liter after OCT (P < 0.05) and –65%, plasma GH levels 17.7 ± 1.7 µg/liter after SOM230 (P < 0.01), both vs. 50.8 ± 4.5 µg/liter on CD]. A comparable suppressive effect on GH levels by 250 µg OCT and SOM230 was observed in a total of eight patients. In this subgroup of eight equal responders, both SOM230 and OCT significantly suppressed GH levels by 65 ± 7% (8.0 ± 2.7 vs. 20.4 ± 6.5 µg/liter on CD, P < 0.05) and 72 ± 7% (7.5 ± 3 vs. 20.4 ± 6.5 µg/liter on CD, P < 0.05; OCT vs. SOM230, P = not significant), respectively (Fig. 3A).

The second pattern of response to the study drugs, observed in a subgroup of three patients, is illustrated by the 24-h GH profile of patient 12 (Fig. 2B). In this particular patient, no decline in circulating GH concentrations after OCT administration was seen (mean plasma GH level 76.7 ± 7.3 vs. 67.4 ± 4.8 µg/liter on CD). However, a significant suppression of serum GH levels after administration of SOM230 was found (–68%; 21.9 ± 2.2 µg/liter vs. 67.4 ± 4.8

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interestingly, in this particular patient the observed potent suppression by the high-dose 250 $\mu$g SOM230 was also achieved by the low-dose 100 $\mu$g SOM230 (−64%; 24.4 ± 3.4 $\mu$g/liter). As shown in Fig. 3B, the mean suppression of GH levels in these three patients by SOM230 was significantly greater than the suppressive effect by OCT [−70 ± 2%, 9.7 ± 6 $\mu$g/liter and −17 ± 15%, 30.9 ± 23 $\mu$g/liter, respectively, vs. 30.5 ± 19 $\mu$g/liter on CD (SOM230 vs. CD, $P < 0.01$; SOM230 vs. OCT, $P < 0.05$ and OCT vs. CD, $P = n.s.$)].

Patient 8 demonstrated a third observed response pattern (Fig. 2C), which showed a significant inhibition by OCT (−79%; mean GH level, 2.9 ± 0.7 vs. 13.8 ± 0.6 $\mu$g/liter on CD; $P < 0.01$). SOM230 was not effective during the full 2- to 8-h postinjection time interval to elicit an inhibitory effect on circulating GH concentrations (14.5 ± 1.9 vs. 13.8 ± 0.6 $\mu$g/liter on CD, $P = n.s.$). However, this patient was not insensitive to SOM230 because a short-lasting suppressive effect of SOM230 was established (−40%; mean GH level 1–3 h after administration, 7.2 ± 0.4 vs. 12.4 ± 0.2 $\mu$g/liter on CD; $P < 0.001$). Still, in this short period of time, OCT induced a more powerful 87% suppression of GH con-
centrations (1.6 ± 0.3 μg/liter; OCT vs. CD, *P < 0.001; OCT vs. SOM230, *P < 0.001).

PRL levels of all 12 patients were within the normal range [mean of five blood samples, <25 μg/liter (men) or 44 μg/liter (women); Table 1]. In two patients, plasma PRL levels decreased after sc injection of OCT as well as with SOM230 (data not shown). Interestingly, the 24-h circulating plasma curves of GH and PRL levels in one of these patients was highly correlated on CD and at treatment days with OCT and SOM230 (r = 0.77, 0.99, and 0.95, respectively, all *P < 0.001), which suggests a mixed GH/PRL-secreting pituitary adenoma that cosecreted both hormones from the same adenoma cell.

Figure 4 shows the mean glucose and insulin concentrations of 11 patients (patient 4 was excluded because he was an insulin-treated patient with type 2 diabetes), starting 3 h after sc administration until 2 h after lunch, compared with the same period of time on CD. Compared with the mean glucose level at 1200 h (3 h after dose) on CD (4.4 ± 0.2 mmol/liter; OCT (*P < 0.05, 0.3 mmol/liter; 250 μg SOM230; 7.1 ± 0.6 mmol/liter; and 100 μg SOM230, 6.8 ± 0.4 mmol/liter)). The highest plasma glucose levels were 10.8 and 13.1 mmol/liter 5 h after injection of OCT and 250 μg SOM230, respectively, and were both observed in patient 1, who was known to have an impaired glucose tolerance (assessed by oGTT before start of the trial). Overall, there was a trend that OCT and both SOM230 dosages induced a comparable increase in mean glucose levels, that responded equally to a meal at 1230 h, compared with CD.

OCT induced an inhibitory effect on mean plasma insulin levels compared with CD, which sustained until 2 h after lunch (1200–1430 h; *P < 0.05). Mean insulin levels seemed not to be affected by both SOM230 dosages because also after lunch a similar increase in insulin levels was observed as on CD (Fig. 4B). Patient 12 had severe insulin resistance. On the CD, 30 min after lunch was consumed, a sharp increase in plasma insulin levels to a maximum 348 mU/liter was found. This was even more pronounced after 250 μg SOM230 was administered, when insulin levels rose to a maximum of 903 mU/liter (1 h after lunch). However, the blood glucose concentrations of this patient remained within the range of the other nondiabetic patients (Fig. 4A).

In vitro studies

Apart from the direct effects of OCT and SOM230 on GH release by cultured pituitary tumor cells from two patients, the native peptide SS was also tested. GH production in the control wells from the adenoma cells of patients 6 and 12 after a 72-h incubation amounted to 228 ± 40 and 312 ± 18 ng/dish, respectively. In agreement with the in vivo response of patients 6 and 12 (Fig. 2, A and B, respectively), 10 nM SOM230 lowered significantly GH secretion by ∼32.7 ± 6.8 and ∼23 ± 6.9% in the primary tumor cell cultures of patients 6 and 12, respectively (*P < 0.05 in both instances), whereas 10 nM OCT inhibited only the GH secretion in the adenoma cells of patient 6 (∼26.1 ± 10.5%; *P < 0.05; Fig. 5A). SS lowered GH secretion in both primary cultures as well...
with OCT. The acute effects of a single dose of 250 g SOM230 and 100 g OCT in circulating GH concentrations demonstrated three patterns of response in the 12 patients investigated. In eight patients, both SS analogs were equally effective in lowering GH levels. This suggests that in these patients the sst2 subtype is the major receptor on the pituitary adenoma, which is responsible for mediating these inhibitory effects. It is well known that sst2 especially is involved in the inhibitory actions of SS and SS analogs on hormone secretion, both in primary cultured human fetal pituitary cells and GH-secreting pituitary adenoma cells as well (12, 20). The relative amount of mRNA expression levels of this receptor subtype was positively correlated with the sensitivity to OCT treatment in vivo (21). The in vitro data of patient 6 illustrate in this group of equal responders that the relatively high mRNA level for sst2 combined with the good affinity of both SOM230 and OCT account for the suppressive effects of both drugs on GH secretion in this group of patients. SOM230 has a 2.5 times lower affinity to sst2 than OCT, which explains the similar effect of 250 g SOM230 and 100 g OCT in this category of acromegalic patients.

The second pattern of response, illustrated by patient 12 in which SOM230 is far more efficacious, compared with OCT in suppressing GH levels, was observed in three patients. A pivotal role for sst2 in mediating suppression of GH release is probable. The in vitro data of patient 12 show relatively low mRNA expression levels for sst2 and higher expression levels for sst5. The IC50 for sst5 of SOM230 is 0.16 nmol/liter, and that of OCT is 40 times higher (6.3 nmol/liter), pointing to the higher affinity of SOM230 for the sst5 subtype. These observations, together with the the in vitro significant inhibition by the native SS on the primary culture of adenoma cells, suggest that both SS and SOM230 exert their potent effects in this particular tumor via sst2 subtype. So far, the role of sst2 in mediating GH release was investigated only in studies with primary cultures of pituitary adenoma cells obtained from acromegalic patients (20, 21). Saveanu et al. (15) found a 30-fold higher expression of sst2 mRNA, compared with sst5 mRNA, in four adenomas poorly responsive to OCT. The addition of the sst5-specific analog BIM23268 to the medium achieved a maximal GH suppression. This suggests a rescue through sst5 when tumors are only partially sensitive to OCT (15). SOM230 induced a 3-fold stronger inhibition than OCT on GH release by cultured rat pituitary cells and a pronounced inhibition of plasma IGF-I levels in rodents after 18 wk of treatment, which again is suggestive for sst5 involvement (16).

We present the first clinical evidence that the sst5 subtype may indeed play an essential role in mediating the in vivo suppressive actions by SOM230 on GH concentrations in three acromegalic patients, which were (partially) unresponsive to OCT. Because SOM230 is able to lower GH levels in both subgroups of patients, coupled with sst2 and sst5 subtype physiology, respectively, this novel SS analog has a clear advantage over OCT and might increase the number of patients who can be biochemically controlled during long-term medical treatment. Furthermore, in patient 12, 100 and 250 μg SOM230 suppressed GH levels equally. In this particular case, increasing the SOM230 dosage by a factor 2.5 did not result in a further increase in GH inhibition. This phenomenon is already known for patients who are sensitive to OCT treatment: a similar GH suppression is found on sc injections with OCT dosages in the range of 100-1500 μg/d (22, 23). This could indicate that the density of the predominantly expressed sst determines the response to a SS analog: in GH-secreting adenomas expressing sst2 in high density, OCT is able to suppress GH levels significantly. However, if sst2 is almost not expressed on the pituitary adenoma, sst5 mediates the GH-suppressive effects of SS and SS analogs. The dose-response curves of OCT and SOM230 seem to reach the plateau at low levels when high densities of sst2 and sst5, respectively, are expressed. In vivo and in vitro data from this trial emphasize that the inhibitory effects on GH release by SS and its analogs are primarily mediated via sst2, as seen in the group of eight equal responders to OCT and SOM230. However, when sst2 over sst5 mRNA levels are being expressed below a certain threshold, as in patient 12, a suppressive action on GH concentrations via sst2 receptors becomes visible. In addition, heterodimeric effects of different sst subtypes are suggested to play a role in receptor physiology (24, 25), and, as discussed previously, the BIM23244 bispecific sst2,sst5 analog has already shown to be more active than the combination of a sst2-specific analog combined with a sst5 specific analog on GH release (15, 26), indicating that a heterodimeric effect by SOM230 on sst2 and sst5 subtypes cannot be ruled out.

The third response was observed in one patient, who only transiently responded to SOM230, whereas OCT was far more efficacious in lowering GH levels. The most likely explanation is the presence of a relatively high sst and a low sst5 mRNA expression level, resulting in a high sensitivity for OCT. Whether higher dosages of SOM230 would indeed
induce similar lowering actions on GH concentrations as seen by OCT, remains uncertain.

Because SS and its analogs inhibit the secretion of insulin, impaired postprandial glucose tolerance was observed after the acute administration of OCT (27). Similar elevations of glucose concentrations were observed after SOM230. However, the elevated glucose levels seem not be caused by an inhibitory action on insulin release because after SOM230 administration at 0900 h, an almost identical insulin response was observed after lunch as on the CD. At present, the mechanism of this transient increase in glucose levels remains uncertain. Several studies support a role for sst2 to control insulin secretion in rats, mice, and humans, whereas sst5 mediates glucagon secretion from the pancreatic α-cells (28–31). On the basis of the SOM230 and OCT affinity profiles for sst2 and sst5, it seems unlikely that OCT, binding 40-fold less to sst5 compared with SOM230, would exert such a strong and long-lasting insulin inhibition via sst5 subtype, whereas SOM230 treatment resulted in barely any inhibition. Therefore, these opposed effects of OCT and SOM230 on insulin levels suggest a pivotal role for sst2 subtype in regulating human insulin secretion. In cynomolgus monkeys, insulin, glucagon, and glucose levels remained unchanged during 7 d of high-dose infusion with SOM230. Furthermore, during an 18-wk treatment with pharmacological doses of SOM230, plasma glucose levels were not changed, indicating that SOM230 is well tolerated in rats and monkeys with regard to glucose homeostasis (16, 32).

The promising pharmokinetic properties of SOM230 found in vivo in rats, accounting for a terminal elimination half-life of 27 h compared with 2 h for OCT (16), did not result in a longer duration of action of SOM230 than that of OCT. Probably, serum SOM230 concentrations drop sooner below a certain therapeutic level, leading to a duration of action on GH levels comparable with that of OCT treatment.

In conclusion, our data suggest that SOM230 has the potency to increase the number of acromegalic patients who can be biochemically controlled during long-term treatment because of its additional suppressive effects on GH secretion via sst5. However, the subtype sst5 seems to be the dominant receptor in controlling hypersecretion in acromegaly. No serious side effects occurred during SOM230 treatment. The sudden increase in glucose levels after SOM230 injection needs additional attention and cannot be explained by sst2- or sst5-mediated action on insulin secretion. Future studies will also address the question of whether SOM230 can control pituitary adenoma size in acromegaly better than OCT (9). Besides sst5 and sst2, sst1 and sst3 also seem to be involved in cell proliferation and the induction of apoptosis (33–36). This suggests that the universal SS analog SOM230, with good affinity for both sst1 and sst3, might have possible antiproliferative and tumor size reducing effects as well.

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