Pasireotide (SOM230) Demonstrates Efficacy and Safety in Patients with Acromegaly: A Randomized, Multicenter, Phase II Trial

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Context: Pasireotide (SOM230) is a novel multireceptor ligand somatostatin analog with affinity for somatostatin receptor subtypes sst_{1-3} and sst_5. Because most GH-secreting pituitary adenomas express sst_2 and sst_5, pasireotide has the potential to be more effective than the sst_2-preferential somatostatin analogs octreotide and lanreotide.

Objective: Our objective was to evaluate the efficacy and safety of three different doses of pasireotide in patients with acromegaly.

Design: We conducted a phase II, randomized, multicenter, open-label, three-way, crossover study.

Patients: Sixty patients with acromegaly, defined by a 2-h five-point mean GH level higher than 5 μg/liter, lack of suppression of GH to less than 1 μg/liter after oral glucose tolerance test, and elevated IGF-I for age- and sex-matched controls. Patients could have had previous surgery, radiotherapy, and/or medical therapy or no previous treatment.

Intervention: After treatment with octreotide 100 μg sc three times daily for 28 d, each patient received pasireotide 200, 400, and 600 μg sc twice daily in random order for 28 d.

Main Outcome Measure: A biochemical response was defined as a reduction in GH to no more than 2.5 μg/liter and normalization of IGF-I to age- and sex-matched controls.

Results: After 4 wk of octreotide, 9% of patients achieved a biochemical response. After 4 wk of pasireotide 200–600 μg sc bid, 19% of patients achieved a biochemical response, which increased to 27% after 3 months of pasireotide; 39% of patients had a more than 20% reduction in pituitary tumor volume. Pasireotide was generally well tolerated.

Conclusions: Pasireotide is a promising treatment for acromegaly. Larger studies of longer duration evaluating the efficacy and safety of pasireotide in patients with acromegaly are ongoing. **(*J Clin Endocrinol Metab* 95: 2781–2789, 2010)**

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Abbreviations: bid, Twice daily; CI, confidence interval; FBG, fasting blood glucose; HbA_{1c}, glycosylated hemoglobin; LAR, long-acting release; MRI, magnetic resonance imaging; tid, three times daily.

Acromegaly is a rare, serious condition characterized by chronic hypersecretion of GH, caused by a GH-secreting pituitary adenoma in more than 90% of patients (1). GH induces the synthesis of IGF-I, and elevated GH and IGF-I levels cause metabolic dysfunction and somatic growth, resulting in significant morbidity and mortality (2).

Transsphenoidal surgery is the first-line option for patients with acromegaly (3). However, most patients have macroadenomas, and surgical cure rates in these patients decrease with increasing tumor diameter and extrasellar extension (4). Most patients with a macroadenoma will require adjuvant medical therapy or radiotherapy to achieve disease control.

Somatostatin analogs, the mainstay of medical therapy for patients with acromegaly, have been traditionally used after surgery but more recently as first-line therapy in selected patients (5). Control of GH or IGF-I with adjuvant somatostatin analog therapy is achieved in 48–67% of patients (6). In recent studies of first-line therapy with octreotide long-acting release (LAR) in patients with *de novo* acromegaly, combined control of GH and IGF-I after 24 wk of treatment was achieved by approximately 25% of patients (7, 8). Approximately 90% of GH-secreting pituitary tumors express somatostatin receptor subtypes 2 and 5 (sst_2 and sst_5), which signal the pituitary gland to suppress GH secretion (1). Octreotide and lanreotide both act preferentially via sst_2 and have lower affinity for sst_5 (9).

Pasireotide (SOM230) is a novel multireceptor ligand somatostatin analog with a unique receptor binding profile, having high affinity for sst_{1-3} and sst_5. Compared with octreotide, pasireotide has an *in vitro* binding affinity 40-, 30-, and 5-fold higher for sst_5, sst_1, and sst_3, respectively, and 2-fold lower for sst_2 (9). Because of the broader somatostatin receptor binding profile of pasireotide, and the known somatostatin receptor subtype expression of GH-secreting pituitary adenomas, pasireotide has the potential to be more effective than sst_2-preferential somatostatin analogs.

Results from an earlier proof-of-concept study showed that single doses of sc pasireotide of 100 and 250 μg suppressed GH and IGF-I levels in a dose-dependent manner in 12 patients with acromegaly (10). Furthermore, although GH was suppressed to a similar extent with pasireotide and octreotide in eight patients, a significantly greater GH suppression was seen with pasireotide in three patients (10). This result suggested that pasireotide has the potential to increase the number of patients with acromegaly who can achieve biochemical control during long-term medical treatment.

This paper presents results from a phase II, randomized, multicenter, open-label, three-way, crossover study in patients with active acromegaly that assessed the efficacy, safety, and pharmacokinetics of three different doses of pasireotide.

Patients and Methods

Patients

Eligible patients were aged at least 18 yr and had active acromegaly due to a pituitary adenoma, confirmed by a 2-h five-point mean GH level higher than 5 μg/liter, lack of suppression of GH nadir to less than 1 μg/liter after oral glucose tolerance test, and elevated IGF-I for age- and sex-matched controls. Patients could have had previous surgery, radiotherapy, and/or medical therapy or could have been previously untreated (*de novo*). For patients who had previously received medical therapy for acromegaly, the washout periods before study entry were 16 wk for long-acting formulations of somatostatin analogs, 1 wk for octreotide sc, 4 wk for dopamine agonists, and 4 wk for GH receptor antagonists.

Key exclusion criteria were tumor compression of the optic chiasm causing visual field defects, a requirement for surgical intervention for relief of any sign or symptom associated with tumor compression, radiotherapy in the past 2 yr, significant cardiovascular morbidity (*e.g.* congestive heart failure or unstable angina), symptomatic cholelithiasis, and liver disease.

The study was conducted in accordance with the Declaration of Helsinki, and an independent ethics committee or institutional review board for each study site approved the study protocol. All patients provided written informed consent to participate in the trial.

Study design

This was a randomized, open-label, crossover, multicenter study. All patients self-administered octreotide 100 μg sc three times daily (tid) for 28 d to assess response to standard treatment. After octreotide treatment, each patient received pasireotide 200, 400, and 600 μg sc twice daily (bid) in random order for 28 d. Thus, all patients received the three different doses of pasireotide (Fig. 1).

Endpoints

For each patient, there was a treatment period with octreotide and three treatment periods with different pasireotide doses. The first efficacy endpoint was evaluated at the end of the first pasireotide treatment period. The second efficacy endpoint was evaluated at the end of the third treatment period.

The primary efficacy outcome was a binary response variable based on circulating GH and IGF-I levels. A patient was considered to have achieved a full biochemical response if mean GH measured 1, 1.5, and 2 h after administration of study drug was no more than 2.5 μg/liter and if mean IGF-I 30 and 1 min before study drug administration was within normal limits for age- and sex-matched controls.

Levels of circulating GH and IGF-I were also evaluated separately to compare between treatment groups as a secondary efficacy endpoint at the end of treatment period 1.

Pituitary magnetic resonance imaging (MRI) scans were obtained at screening and after the last pasireotide dose and included T1-weighted sagittal and coronal, enhanced and unenhanced sequences. Digital images were assessed using established

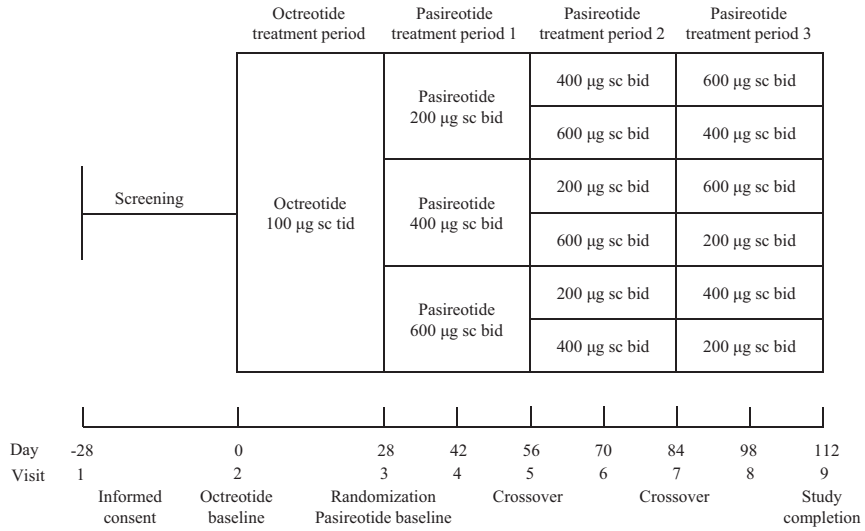

FIG. 1. Study design.

techniques and criteria by a central neuroradiologist (University of Edinburgh Neuroradiology) blinded to the dose sequence (8). A pituitary tumor volume change of >20% from screening was considered significant, because the estimated measurement error threshold was 20%. Although the specification of micro- *vs.* macroadenoma was not reported as part of the study protocol, this information pertaining to the 14 *de novo* patients was provided by the central reader (A.J.F.) as a *post hoc* analysis.

Secondary evaluations included changes in the signs and symptoms of acromegaly at the end of each treatment period. Sleepiness was assessed using the Epworth Sleepiness Scale (11). Headache, perspiration, paresthesia, fatigue, osteoarthralgia, and carpal tunnel syndrome were scored according to a five-point scale (0, absent; 1, mild; 2, moderate; 3, severe; 4, very severe). Safety assessments consisted of monitoring and recording all adverse events and serious adverse events; the regular monitoring of hematology, blood chemistry, and urinalysis parameters; regular measurement of vital signs; the performance of physical examinations; and body weight measurements. Blood samples for laboratory tests, including blood glucose measurements, were taken at each visit under fasted conditions before the morning dose of study drug.

Hormone assays

Serum GH and IGF-I were measured by a central laboratory using validated chemiluminescent immunometric assays (DPC Immulite 2000; Diagnostic Products Corp., Los Angeles, CA). The lower limit of detection for GH was 0.1 μg/liter with intra- and interassay coefficients of variation less than or equal to 10%. For IGF-I, the lower limit of detection was 25 μg/liter with intra- and interassay coefficients of variation less than or equal to 8.3%. Normal values for IGF-I are 182–780, 114–492, 90–360, and 71–290 μg/liter in patients aged 16–24, 25–39, 40–54, and 55 yr and older, respectively.

Pharmacokinetics

Blood collections for the pharmacokinetic analysis were performed at time 0 (predose) and 1 and 2 h after pasireotide administration on d 28, 42, 56, 70, 84, 98, and 112. Descriptive statistics were provided for the minimum pasireotide concentration, the maximum pasireotide concentration, and the average pasireotide concentration during the first 2 h after dose on wk 2 and 4 of each pasireotide treatment period, grouped by dose. Plasma concentrations of pasireotide were measured using a validated RIA with a lower limit of detection of 0.04 ng/ml.

Statistical analyses

Generalized linear and mixed models were fitted for continuous and binary data. The models included dose level and sequence as fixed effects and subject as a random effect. Due to the small number of patients per center, all data were pooled, and center effects were not included in the statistical models. At the end of treatment period 1, estimated treatment contrasts for binary data are presented as odds ratios and associated 95% confidence intervals (CI).

For the first efficacy endpoint at the end of pasireotide treatment period 1, patient response status was analyzed using logistic regression models with treatment (each of the pasireotide dose groups) as an independent variable and the GH and IGF-I levels before the pasireotide treatment as baseline covariates. No transformations to pasireotide baseline covariates were applied.

For the second efficacy endpoint at the end of pasireotide treatment period 3, patient response status was analyzed using a logistic regression model employing treatment as a fixed effect and subject as a random effect, with adjustment for pasireotide baseline GH and IGF-I levels. No transformations to pasireotide baseline covariates were applied.

P values from paired, one-sided *t* tests are reported for changes in GH and IGF-I after octreotide or pasireotide treatment. The tests were not adjusted for multiplicity because of the exploratory nature of the study.

Results

Twenty-three clinical centers worldwide enrolled 61 patients aged at least 18 yr with active acromegaly, of whom 60 received both octreotide sc and at least one dose of pasireotide sc (Table 1). Eight patients discontinued treatment prematurely. One patient discontinued during octreotide therapy because of an adverse event, and seven patients discontinued during pasireotide treatment: four withdrew because of an adverse event; two withdrew consent; and one was withdrawn because of a protocol violation.

Fifty-eight patients received at least one dose of pasireotide and had a GH and IGF-I measurement at the end of treatment period 1. At the end of treatment period 3, 51 patients had GH and IGF-I evaluations, 51 patients had a GH evaluation, and 53 patients had an IGF-I evaluation. All patients who received at least one dose of pasireotide

TABLE 1. Baseline characteristics of the safety population

Variable	Safety population (n = 60)
Sex, n (%)	
Male	33 (55.0)
Female	27 (45.0)
Mean age, yr (range)	44.2 (18–84)
Race, n (%)	
Caucasian	54 (90.0)
Asian	1 (1.7)
Other	5 (8.3)
Time since diagnosis, n (%)	
<1 yr	21 (35.0)
1–5 yr	18 (30.0)
5 to <10 yr	12 (20.0)
≤10 yr	9 (15.0)
Prior surgery, n (%)	35 (58.3)
Prior radiation, n (%)	9 (15.0)
Surgery or radiation therapy only,[a] n (%)	4 (6.7)
Prior medical therapy, n (%)	42 (70.0)
De novo[b]	14 (23.3)
Dopamine agonist	19 (31.7)
GH receptor antagonist	6 (10.0)
Somatostatin analog	40 (66.7)
Adjuvant	30 (50.0)
First line	10 (16.7)
No somatostatin analogs[c]	6 (10.0)

[a] No medical treatment but previous surgery or radiation therapy.

[b] No previous medical, surgical, or radiation therapy.

[c] Previous medical, surgical, or radiation therapy but no somatostatin analog treatment.

(n = 60) were included in the safety analysis. Fifty-one patients had both baseline and follow-up pituitary MRI scans and were included in the MRI analysis.

Of the 61 enrolled patients, eight were accepted into the study with either a GH or IGF-I level that did not meet the inclusion criteria [*i.e.* a GH level ≤5 μg/liter (n = 4) or an IGF-I level below the upper limit of normal (n = 3) or no baseline measurement (n = 1)]; all four patients with a GH level that did not meet entry criteria had a GH level higher than 2.5 but not higher than 5 μg/liter. These eight patients were enrolled at the investigators' discretion, because it was believed they would benefit from treatment. The primary efficacy analysis is presented with (n = 58) and without (n = 50) these patients.

The majority of patients (77%) had received previous treatment for acromegaly; 23% of patients had *de novo* disease (Table 1). Nine patients had received previous radiation therapy. The time between the last dose of radiation and initiation of treatment with pasireotide ranged from approximately 2.5–25 yr (median duration of 5.3 yr).

Effect of octreotide on GH and IGF-I levels

At baseline, GH levels ranged from 2.8–454 μg/liter (mean 35.5 μg/liter; median 11.28 μg/liter). After 1 month of octreotide 100 μg sc tid, five of 58 patients (9%) achieved a full biochemical response (GH ≤2.5 μg/liter and normal IGF-I levels), 26% had GH not higher than 2.5 μg/liter, and 20% had normal IGF-I levels. The mean ± SD GH level decreased from 35.5 ± 77.9 to 16.4 ± 51.9 μg/liter [mean change, −18.3 μg/liter ($P = 0.007$; 95% CI = −32.7 to −3.9)]. The mean ± SD IGF-I level decreased from 830 ± 206 to 632 ± 245 μg/liter [mean change, −203 μg/liter ($P < 0.0001$; 95% CI = −255 to −152)].

Effect of pasireotide on GH and IGF-I levels

Efficacy at the end of treatment period 1

At the end of treatment period 1 (*i.e.* after 1 month of octreotide 100 μg sc tid and 1 month of pasireotide 200, 400, or 600 μg sc bid), 11 of 58 patients (19%) achieved a full biochemical response, 40% had a GH level not higher than 2.5 μg/liter, and 26% achieved a normal IGF-I level. The mean ± SD GH level decreased slightly from 16.4 ± 51.9 μg/liter at the pasireotide baseline (after octreotide treatment) to 15.1 ± 48.7 μg/liter [mean change, −1.5 μg/liter ($P = 0.16$; 95% CI = −4.4 to 1.5)]. IGF-I decreased from 632 ± 245 to 594 ± 224 μg/liter [mean change, −43.6 μg/liter ($P = 0.017$; 95% CI = −83.6 to −3.6)] after 1 month of treatment. With respect to pretreatment values, mean GH decreased from 35.5 ± 77.9 to 15.1 ± 48.7 μg/liter, and mean IGF-I decreased from 830 ± 206 to 594 ± 224 μg/liter.

In the individual pasireotide dose groups, 14, 12, and 30% of patients in the pasireotide 200, 400, or 600 μg bid groups, respectively, were full responders; 29, 41, and 50% achieved a GH level not higher than 2.5 μg/liter, and 29, 18, and 30% achieved normalized IGF-I (Fig. 2). There was no significant difference between dose groups in the percentage of patients achieving a full biochemical response or normalized IGF-I levels (Fig. 2), although significantly more patients who received pasireotide 600 μg bid achieved GH of not higher than 2.5 μg/liter than patients who received pasireotide 200 μg bid [odds ratio = 17.3 (95% CI = 2.25–390); $P = 0.019$]. Although full and partial biochemical responses to pasireotide tended to be higher among those who received the highest dosage, no clear dose relationship was apparent.

Efficacy after 3 months of treatment with pasireotide

The mean ± SD GH and IGF-I levels decreased from 16.4 ± 51.9 and 632 ± 245 μg/liter at the pasireotide baseline (after octreotide treatment) to 7.6 ± 13.6 and 551 ± 252 μg/liter, respectively, after 3 months of treatment with pasireotide [mean change, −2.1 μg/liter for GH ($P = 0.0546$; 95% CI = −4.7 to 0.5) and −76 ± 21

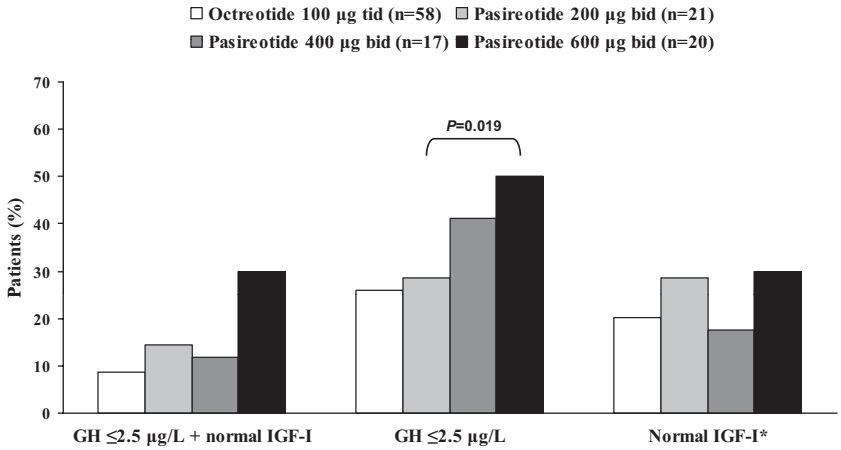

FIG. 2. Percentage of patients who achieved a GH, IGF-I, or GH plus IGF-I response after 1 month of treatment with octreotide or pasireotide, by dose. All patients received octreotide 100 μg tid for 1 month followed by 1 month of pasireotide 200, 400, or 600 μg bid. Results are after 1 month octreotide and 1 month octreotide plus 1 month pasireotide are presented here. *, For IGF-I alone, there was an additional patient included in the analysis for octreotide (n = 59).

μg/liter for IGF-I ($P = 0.0003$; 95% CI = −117.8 to −34.2])].

At the end of treatment period 3, 14 of the 51 patients (27%) with a GH and IGF-I measurement had achieved a full biochemical response at that time point, 25 of 51 (49%) had GH not higher than 2.5 μg/liter, and 20 of 53 (38%) achieved normalized IGF-I.

Overall, 20 of the 58 patients (34.5%) in the efficacy analysis were biochemical responders at the end of any of the three treatment periods (*i.e.* irrespective of the sequence of dosing). A GH level not higher than 2.5 μg/liter was achieved by 51.7% of patients, and normal IGF-I levels were achieved by 44.8% of patients.

An analysis of full biochemical response during the entire study period irrespective of the sequence of dosing, but excluding the eight patients who did not meet inclusion criteria, yielded similar results; *i.e.* 18 of 50 patients (36%) were full biochemical responders, and 50 and 44% of patients achieved a GH level not higher than 2.5 μg/liter and normal IGF-I levels, respectively.

Evaluation of tumor response

The mean ± SEM baseline tumor volume was 4917 ± 960 mm^3 (range 55–36,256 mm^3). The mean tumor volume at study end was 4381 ± 983 mm^3 (range 51–38,014 mm^3). The mean ± SEM tumor volume reduction was 512 ± 209 mm^3, and the mean ± SEM percent reduction in pituitary tumor volume was 14.5 ± 2.5%.

Of the 51 patients (including seven who did not meet the GH and IGF-I inclusion criteria) with MRI screening-visit scans and scans at study end, 20 patients (39%) experienced a significant (>20%) reduction in pituitary tumor volume (Fig. 3). No patient had a significant (>20%) increase in pituitary tumor volume.

Effect of pasireotide on signs and symptoms

A reduction in the incidence and severity of the signs and symptoms of acromegaly was seen at study end compared with baseline. The percentage of patients who were headache free was greater at study end compared with baseline, and an overall trend for a reduction in the severity of headache was observed during treatment. A similar pattern was seen for fatigue, perspiration, osteoarthralgia, carpal tunnel syndrome, and paresthesia (Table 2). Overall, there was no treatment effect on the total Epworth sleepiness scale score.

Pharmacokinetic assessment

The pharmacokinetic results indicated that steady-state concentrations of pasireotide were achieved within 2 wk of treatment initiation in patients with acromegaly (Table 3). The maximum pasireotide concentrations at steady state were generally observed at 1 h after dose, as per the sampling schedule. Pharmacokinetic exposures were approximately dose proportional. Plasma concentrations of pasireotide in responders appeared to be higher than those in nonresponders (Table 3), but statistical differences could not be detected due to large variability. At wk 2 and 4 of the first treatment period, predose concentrations of pasireotide were 1.26 ± 0.89 μg/liter (n = 21) and 1.24 ± 0.63 μg/liter (n = 20) in the 200-μg group, 1.99 ± 1.19 μg/liter (n = 18) and 1.79 ± 1.10 μg/liter (n = 17) in the 400-μg group, and 3.12 ± 1.58 μg/liter (n = 20) and 3.44 ± 1.86 μg/liter (n = 20) in the 600-μg group, respectively.

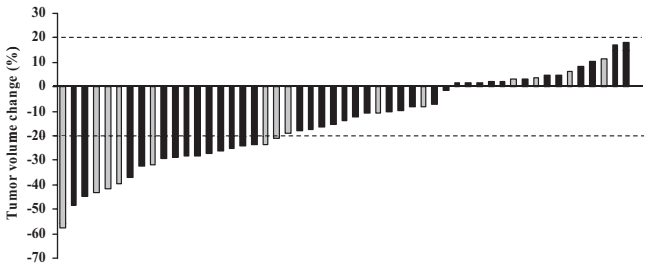

FIG. 3. Percentage change in pituitary tumor volume from baseline (before octreotide treatment) to the end of the study after 3 months of pasireotide treatment in the 51 assessable patients. The 14 *de novo* patients, all of whom had a macroadenoma, are *highlighted in gray*.

TABLE 2. Percentage of patients with acromegaly symptom scores of 0-4 at baseline (before receiving octreotide) and at study end after 3 months of pasireotide treatment

	Baseline (before octreotide), n = 59					End of study, n = 59				
Symptom score[a]	0	1	2	3	4	0	1	2	3	4
Headache (%)	28.8	16.9	30.5	16.9	5.1	33.9	40.7	16.9	1.7	1.7
Fatigue (%)	15.3	27.1	32.2	16.9	6.8	20.3	35.6	25.4	10.2	3.4
Perspiration (%)	22.0	18.6	32.2	18.6	6.8	32.2	39.0	18.6	3.4	1.7
Osteoarthralgia (%)	32.2	22.0	23.7	11.9	8.5	35.6	28.8	22.0	3.4	5.1
Carpal tunnel syndrome (%)	55.9	11.9	22.0	5.1	3.4	69.5	11.9	8.5	0	3.4
Paresthesia (%)	37.3	28.8	20.3	10.2	1.7	64.4	20.3	5.1	1.7	3.4

[a] 0, None/absent; 1, mild; 2, moderate; 3, severe; 4, very severe.

Safety and tolerability

Fifty-two of the 60 patients (87%) in the pasireotide safety population experienced one or more adverse event, with 45 patients (75%) considered to have experienced study drug-related adverse events (Table 4). No patient died during the study. Mild-to-moderate gastrointestinal disturbances, *e.g.* diarrhea, nausea, and abdominal pain were the most frequently reported adverse events during pasireotide therapy. Adverse events with a suspected study-drug relationship occurring during pasireotide treatment included nausea (25%), diarrhea (22%), abdominal pain (12%), flatulence (10%), increased blood glucose (7%), increased glycosylated hemoglobin (HbA_{1c}) (5%), and diabetes mellitus (5%) (Table 4).

Three patients experienced a serious adverse event during treatment with pasireotide (hyponatremia, osteoarthritis, and pregnancy); none were considered related to pasireotide.

Four patients discontinued treatment because of adverse events: one patient with preexisting diabetes mellitus who experienced worsening glycemic control; one patient with preexisting diabetes mellitus with an increase in HbA_{1c}; one patient with a gastrointestinal disorder, nausea, and somnolence; and one patient who became pregnant. All the adverse events that led to treatment discontinuation, except for the pregnancy, were considered related to pasireotide.

At baseline, 38 patients had normal fasting blood glucose (FBG) values (<5.6 mmol/liter, as described by the American Diabetes Association criteria, 2004), 17 patients had impaired glucose tolerance (FBG 5.6 to <7.7 mmol/liter), and four patients had FBG of 7 mmol/liter or higher (Table 5). Of the 38 patients with normal FBG at baseline, 28 remained within the normal range at end of study, seven had an increase in FBG into the 5.6 to less than 7 mmol/liter range, and three had an increase in FBG to 7 mmol/liter or higher (Table 5). Of the 17 patients with impaired glucose tolerance at baseline, two had normal FBG at study end and nine had an increase in FBG to 7 mmol/liter or higher. The four patients with baseline FBG of 7 mmol/liter or higher remained in this category. At study end, 30 patients had normal FBG, 13 had impaired FBG, and 16 had FBG of 7 mmol/liter or higher.

TABLE 3. Pharmacokinetic parameters at wk 2 and 4 of pasireotide 200, 400, and 600 μg sc bid in responders and nonresponders

	wk 2		wk 4	
Dose	Responders[a]	Nonresponders	Responders[a]	Nonresponders
200 μg sc bid	n = 6	n = 49	n = 7	n = 47
C_{min} (μg/liter)	2.12 (3.12 ± 3.54)	1.43 (1.46 ± 0.81)	2.27 (2.77 ± 2.96)	1.45 (1.54 ± 0.84)
C_{max} (μg/liter)	6.85 (9.15 ± 6.28)	5.45 (6.05 ± 2.86)	7.65 (8.09 ± 2.67)	6.00 (6.72 ± 3.92)
C_{avg} (μg/liter)	5.24 (7.19 ± 5.52)	4.26 (4.48 ± 1.98)	5.44 (6.11 ± 2.31)	4.44 (5.07 ± 2.93)
400 μg sc bid	n = 10	n = 42	n = 13	n = 41
C_{min} (μg/liter)	2.28 (2.32 ± 1.10)	2.31 (2.50 ± 1.85)	3.04 (2.80 ± 1.30)	2.41 (2.70 ± 2.07)
C_{max} (μg/liter)	10.9 (11.3 ± 3.07)	11.6 (11.4 ± 4.5)	14.3 (13.0 ± 3.50)	9.43 (10.1 ± 4.58)
C_{avg} (μg/liter)	8.06 (8.49 ± 2.27)	8.70 (8.36 ± 3.24)	9.84 (9.74 ± 2.37)	7.05 (7.61 ± 3.51)
600 μg sc bid	n = 13	n = 40	n = 16	n = 36
C_{min} (μg/liter)	3.59 (5.13 ± 4.84)	3.15 (3.68 ± 2.61)	3.73 (3.88 ± 1.66)	3.31 (3.68 ± 2.53)
C_{max} (μg/liter)	25.5 (25.0 ± 9.04)	16.0 (17.5 ± 7.0)	20.3 (19.5 ± 7.91)	16.75 (17.0 ± 8.18)
C_{avg} (μg/liter)	19.3 (18.6 ± 7.13)	12.2 (12.9 ± 5.0)	15.2 (14.3 ± 5.5)	12.2 (12.6 ± 5.73)

Data are expressed as median (mean ± SD). C_{min}, Minimum pasireotide concentration; C_{max}, maximum pasireotide concentration; C_{avg}, average pasireotide concentration during the first 2 h after dose.

[a] A patient could be reported as a responder at each dose level if they achieved GH not higher than 2.5 μg/liter and normal IGF-1 at wk 2 or 4 of each treatment period.

TABLE 4. Adverse events (with a frequency of at least 5%) with a suspected study-drug relationship occurring during 1 month of treatment with octreotide and 3 months treatment with pasireotide

	Octreotide 100 μg sc tid	Pasireotide 200, 400, or 600 μg sc bid
Any suspected drug-related adverse event	30 (50.0)	45 (75.0)
Nausea	9 (15.0)	15 (25.0)
Diarrhea	20 (33.3)	13 (21.7)
Abdominal pain	5 (8.3)	7 (11.7)
Flatulence	5 (8.3)	6 (10.0)
Blood glucose increased	1 (1.7)	4 (6.7)[a]
Dizziness	1 (1.7)	4 (6.7)
Increased HbA_{1c}	0	3 (5.0)[a]
Vertigo	0	5 (5.0)
Diabetes mellitus	0	3 (5.0)[a]

Data are shown as n (%).

[a] These events are reported in different patients.

At the octreotide baseline, the mean ± SD FBG (n = 60) was 5.6 ± 1.1 mmol/liter. At the pasireotide baseline (*i.e.* after 1 month of octreotide), the mean ± SD FBG (n = 60) was 5.4 ± 1.1 mmol/liter. After 1 month of pasireotide, the mean ± SD FBG (n = 58) was 6.01 ± 1.5 mmol/liter. At study end (n = 58), it was 6.4 ± 2.3 mmol/liter.

Increases in FBG were improved by appropriate diabetic management in all but one patient, who discontinued the study. Metformin was the most commonly used oral hypoglycemic agent; glibenclamide, glipizide, and acarabose were also used.

The mean HbA_{1c} level at the pasireotide baseline was 6.01 ± 0.57% (range 5.0–8.0%) and increased at study end to 6.45 ± 0.84% (range 5.1–8.5%) ($P < 0.0001$).

TABLE 5. Fasting blood glucose levels at baseline and at the end of the study in the 59 patients with post-baseline measurements[a]

Baseline fasting blood glucose level[b]	End of study fasting blood glucose level[c]		
	<5.6 mmol/liter	5.6–7.7 mmol/liter	≥7.7 mmol/liter
<5.6 mmol/liter (n = 38)	28 (73.7)	7 (18.4)	3 (7.9)
5.6–7.7 mmol/liter (n = 17)	2 (11.8)	6 (35.3)	9 (52.9)
≥7.7 mmol/liter (n = 4)	0	0	4 (100)

[a] Data are shown as n (%). Of the 60 patients evaluated for fasting blood glucose levels, one patient did not have a post-baseline measurement and was therefore not included in the analysis.

[b] Based on the American Diabetes Association criteria, 2004.

[c] One patient did not have an end-of-study assessment; the last available value was used (visit 7).

The mean HbA_{1c} level at the octreotide baseline was 5.93 ± 0.60%.

Discussion

The patient population for this study included those patients currently receiving medical therapy for the treatment of acromegaly and those who were not. Gathering information on response to previous treatment with somatostatin analogs was not part of the study protocol and, hence, not rigorously collected. To assess the response to octreotide, it was administered to all patients and not just the subset who had been previously treated with somatostatin analogs. After 28 d of octreotide 100 μg sc tid, a full biochemical response was seen in 9% of patients. This low response rate to octreotide sc therapy may be partly due to the possible inclusion of patients who may have been resistant to previous treatment with somatostatin analogs and to the relatively short treatment period of 1 month.

After the first 4 wk of pasireotide sc treatment, a full biochemical response was seen in 19% of all patients, and after 3 months of treatment, 27% of patients had a full biochemical response, suggesting a continuing reduction in GH and IGF-I levels over the course of the study. Although full and partial responses to pasireotide after 4 wk of treatment tended to be higher among those who received the highest dose, no clear dose-response relationship was apparent. Any attempt to distinguish a dose-response relationship after the second or third month of treatment with pasireotide is potentially confounded by a possible carryover effect between pasireotide doses because there was no washout period.

It is known that the intra-patient variability of the GH response to octreotide plasma concentrations is much smaller than the inter-patient variability (12). It is also known that the effects of octreotide on GH levels after stopping administration of the immediate-release formulation disappear within a few days, and GH secretion returns to pretreatment patterns (13). As such, the risk of a carryover effect from octreotide sc treatment was believed to be negligible. The effects of stopping pasireotide administration on GH levels are not well known. For practical reasons, no washout period was included between octreotide sc treatment and pasireotide administration or between pasireotide treatment periods. The possibility of a carryover effect between pasireotide treatment periods cannot be ruled out, and there may also have been a duration-of-treatment effect due to the additional month of octreotide treatment before pasireotide administration. Because of these factors, an analysis of the effects of pasireotide treatment by dose at the end of 3 months of pa-

sireotide treatment was not considered useful. Additionally, because of the small number of patients in each of the six treatment sequences, an analysis of the effects of the pasireotide treatment sequence on biochemical response was not undertaken. Although *P* values from paired, one-sided *t* tests were calculated for changes in GH and IGF-I after octreotide or pasireotide treatment, it should be noted that this study was not designed, or powered, to compare the effects of pasireotide with those of octreotide. *P* values <0.05 were seen for reductions from baseline in GH and IGF-I after 1 month of octreotide and for further reductions from baseline in IGF-I after both 1 and 3 months of pasireotide treatment.

Pharmacokinetic exposures observed with pasireotide 200, 400, and 600 μg bid were approximately dose proportional. Of interest was that plasma concentrations of pasireotide in responders appeared to be higher than those in nonresponders. However, due to large inter-patient variability, statistical differences were not detected.

Thirty-nine percent of patients had a more than 20% reduction in pituitary tumor volume, and no patient experienced a more than 20% increase in tumor volume. Longer-term studies with octreotide LAR have shown that tumor volume reductions in patients with acromegaly increase progressively over time (8, 14). However, it cannot be excluded that some of the tumor effects seen in the current study may be due to octreotide therapy. Ongoing longer-term studies of pasireotide targeting newly diagnosed patients will help to determine the extent of tumor volume reduction that can be expected.

Octreotide has been in clinical use for the treatment of acromegaly for over two decades and has a well-established safety profile. Common drug-related adverse events seen with somatostatin analogs include mostly mild to moderate and transient injection-site reactions, gastrointestinal disturbances, and hyperglycemia (15). A similar safety and tolerability profile was seen with pasireotide, which was generally well tolerated. The most common adverse effects were mild to moderate gastrointestinal events. Increases in blood glucose are a known effect of somatostatin analog therapy in patients with acromegaly (16–18). Baldelli *et al.* (16) reported that after 6 months of treatment with either lanreotide slow-release or octreotide LAR, the mean HbA_{1c} level significantly increased from $4.7 \pm 0.6\%$ to $5.1 \pm 0.5\%$. Colao *et al.* reported that after the first 6–12 months of therapy with somatostatin analogs, there was a mild increase in HbA_{1c} (between 0.3 and 0.5%) followed by significant reductions after 60 months of therapy (17). Thus, the increase in HbA_{1c} after 4 months of somatostatin analog therapy (1 month with octreotide sc and 3 months with pasireotide sc) seen in this study is similar to the changes reported in the literature. The increases in blood glucose seen in some patients in the current study were generally improved by appropriate diabetic management, when necessary.

In conclusion, 3 months of treatment with sc pasireotide 200–600 μg bid resulted in approximately one third of patients achieving biochemical control as well as 39% of patients achieving a reduction in tumor volume of more than 20%. Pasireotide was generally well tolerated, with adverse gastrointestinal events being the most common. Changes in glycemic parameters seen with pasireotide appear to be consistent with those observed with other somatostatin analogs. These results demonstrate that pasireotide is a promising novel treatment for acromegaly. It is currently unknown whether the observed response rate in this study was influenced by a bias to include especially difficult to treat patients. The potential of pasireotide may become clear only in an ongoing randomized phase III study comparing octreotide and pasireotide.

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