Treatment of psoriasis with chronic subcutaneous administration of somatostatin analog 201-995 (Sandostatin)

I. An open-label pilot study

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■ Increased levels of human growth hormone (HGH) may correlate with the severity of psoriasis and native somatostatin (SRIF) may improve it by inhibiting HGH release. The synthetic SRIF analog, SMS 201-995, is a potent and long-lasting HGH inhibitor. Nine patients with chronic plaque psoriasis completed 12 weeks of open treatment with SMS 201-995. Overall improvement was minimal to marked in six patients and unchanged in three; none worsened. Means of 24-hour pooled HGH (1.7 ± 0.7 μg/L) and fasting plasma somatomedin-C (SM-C) (0.45 ± 0.22 U/mL) were normal at baseline and were not significantly altered by treatment. A high frequency of gastrointestinal side effects occurred, but no patient discontinued treatment because of them. SMS 201-995 may be a useful therapy for psoriasis, but its mechanism of action is unknown. Double-blind placebo-controlled trials are currently in progress to confirm the efficacy of SMS 201-995 in psoriasis.

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NATIVE somatostatin or somatotropin release inhibitory factor (SRIF), a potent inhibitor of human growth hormone (HGH) secretion, is a tetradecapeptide initially isolated from the hypothalamus.[1] It was subsequently shown to be produced by the D cells of both the pancreas and gastrointestinal tract[2] and can be found in the neural elements of the intestinal wall.[3] SMS 201-995, octreotide acetate, is a long-acting synthetic SRIF analog with a half-life of approximately 2 hours compared with 2–4 minutes for SRIF.[4] Furthermore, SMS 201-995 is a more potent and specific inhibitor of HGH release than is SRIF. SMS 201-995 has been employed in the investigational treatment of functional gastrointestinal endocrine tumors,[5,6] gastrointestinal hemorrhage,[7] diabetes mellitus type I,[8] and acromegaly.[9]

The rationale for using an HGH-release inhibitor in the treatment of psoriasis dates back to 1981, when Weber et al[10] hypothesized that there was a direct correlation between serum HGH levels and the extent and severity of psoriasis. They subsequently reported that

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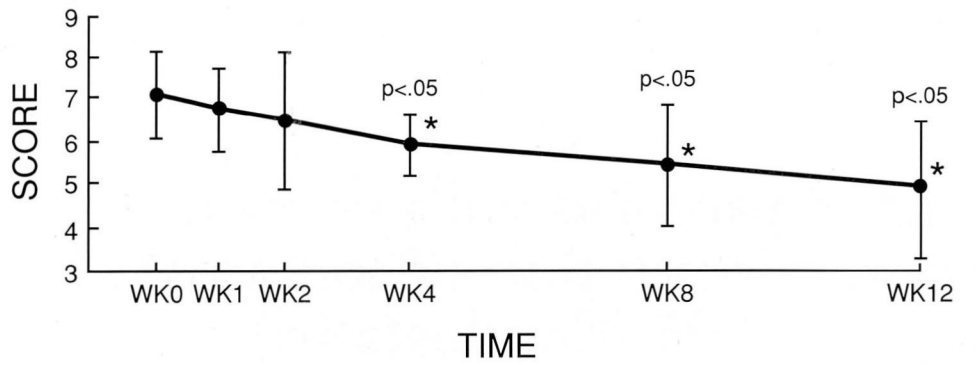

FIGURE 1. The grade of psoriasis (scale, erythema, thickness) over time. See text for details of scoring system. Scale: absent = 0; trace = 1; mild = 2; moderate = 3; severe = 4. Scores for the three symptoms were combined for a total score. Maximum possible score was 12.

improvement was shown in 22 of 26 patients who received SRIF intravenous infusions. They were not able to demonstrate, however, that serum HGH levels, drawn every 2 hours, decreased significantly after treatment.[11] Recently, Matucci-Cerinic et al[12] reported the improvement of psoriatic lesions and arthropathy in 12 of 18 patients and further recommended SRIF treatment in patients with severe skin involvement and polyarthritis.

The rationale for using SMS 201-995 in the treatment of psoriasis can be summarized as follows: (1) SRIF has been reported to improve psoriasis in earlier studies[11,12]; (2) HGH-release inhibitors may decrease HGH as well as other peptides which may be involved in the pathogenesis of psoriasis; (3) SMS 201-995 is concentrated in the target organ (skin) in rats; (4) SMS 201-995 is easy to self-administer by patients taught to give subcutaneous injections; and (5) low toxicity has been demonstrated in normal human volunteers.

The purposes of this open-label pilot study were to: (1) determine whether SMS 201-995 has efficacy in the treatment of psoriasis; (2) determine serum HGH levels before and after treatment with SMS 201-995; (3) measure levels of other peptides which could possibly be affected by SMS 201-995 and which could be involved in the pathogenesis of psoriasis, namely, somatomedin-C (SM-C), substance P, neurotensin, and vasoactive intestinal peptide (VIP); and (4) assess the toxicity of chronic SMS 201-995 administration in otherwise healthy psoriatic subjects.

PATIENTS AND METHODS

Patients

Eleven patients (nine women, two men) with psoriasis (nine stable plaque-type, one guttate, one pustular) participated in the study. Mean age of patients was 36 years (range 21–51 years). The nature of the study was fully explained to all patients according to the protocol approved by the Ohio State University Biomedical Sciences Review Committee for research involving human subjects before obtaining informed consent. The patients had greater than 10% body surface involvement as estimated by a modified rule-of-nines assessment, and were otherwise healthy by history, physical examination, and screening laboratory evaluation.

Treatment protocol

All systemic therapy specifically employed in the treatment of psoriasis was stopped for at least 4 weeks prior to initiating treatment with SMS 201-995. All other topical and phototherapy were stopped for at least 2 weeks prior to treatment. Bland emollients for the body and medicines for psoriatic arthritis and concomitant diseases were permitted as necessary throughout the course of the study. At the end of the washout period and after an overnight fast of 8–10 hours patients were admitted to the Clinical Research Center (CRC) of the Ohio State University Hospitals. Evaluations consisted of complete blood count and differential, routine chemistry, urinalysis, stool fat (72-hour) analysis, peptide hormone levels (except SM-C), skin biopsies, photographs, and subjective gradings at baseline, weeks 1, 4, 6, 8, and 12 of treatment, and 4 weeks after treatment.

Peptide quantitation in blood

Peptide hormones were measured by specific radioimmunoassay of serum with positive controls performed by both the CRC Core Laboratory in conjunction with the Division of Endocrinology and by a commercial laboratory (Metpath, Teterboro, NJ). SM-C, one of a family of insulin-like peptide growth factors thought to mediate

TABLE 1
SUMMARY OF PATIENTS TREATED WITH SMS 201-995 FOR 12 WEEKS

Patient	Age	Sex	Race	Subjective score* BL	Subjective score* WK 12	% Body surface involved† BL	% Body surface involved† WK 12	Global assessment
1	36	F	W	7	4	15	9	Definite improvement
2	38	F	W	7	3	53	9	Marked improvement
3	40	F	W	6	4	34	17	Definite improvement
4	27	M	O	8	6	52	52	No change
5	28	M	W	9	6	38	31	Minimal improvement
6	51	F	B	6	5	18	18	No change
7	48	F	W	8	7	86	87	No change
8	38	F	W	6	6	65	57	Minimal improvement
9	25	F	W	7	3	14	8	Definite improvement

*See Methods for scoring system. Scale: absent = 0; trace = 1; mild = 2; moderate = 3; severe = 4.
†Estimated by modified rule-of-nines.
W = White; O = Oriental; *B* = Black; *BL* = Baseline.

the growth-promoting effect of HGH, is a reliable index of chronic HGH elevation,[13] and was assayed in plasma at baseline and after weeks 4 and 8 of treatment with SMS 201-995.

Clinical evaluation

Psoriatic lesions judged to best represent a particular patient's global disease process were evaluated for scale, erythema, and thickness; each was evaluated on a scale of 0–4 (absent, 0; trace, 1; mild, 2; moderate, 3; severe, 4) with a possible maximum score of 12. The percentage of body surface involvement was estimated, and global assessment of disease was performed at 12 weeks as follows: definitely worse, possibly worse, no change, minimal improvement, definite improvement, marked improvement, almost clear, clear.

Drug administration

SMS 201-995 was administered subcutaneously into uninvolved skin (where possible) of abdomen and thighs every 12 hours for 12 weeks. The initial dose was 50 μg. The dose was increased to 100 μg every 12 hours if after 4 weeks of treatment little to no clinical improvement was noted.

Analysis of data

Repeated measures analysis of variance was performed on the parametric data of the nine patients who completed the first 12 weeks of treatment. In addition, multiple comparisons of the means were performed. The overall mean square error was used to determine which pairs of means were significantly different in each group at the appropriate degrees of freedom with alpha of 0.01. In those instances where a significant difference was noted in the data a paired t-test was used to indicate whether or not this difference existed with the baseline measurement.

For the non-parametric data (psoriasis score, extent, global evaluation), Friedman's 2-way ANOVA was used to indicate if differences in the data existed. For those variables in which a significant difference was found, a Wilcoxon Matched Pairs Signed Rank test was used to indicate differences from baseline (week 0). Data are reported as the mean ± one standard deviation unit.

RESULTS

Eleven patients were enrolled in the study. The data from two patients were not included in the statistical analyses. One of these patients had near complete clearing of psoriasis after 4 weeks of treatment with SMS 201-995 and requested that therapy be discontinued. The other patient, whose psoriasis had been previously controlled with methotrexate, developed a pustular flare of psoriasis during the washout period. Although her condition improved slightly with SMS 201-995, therapeutic response at 2 weeks was insufficient, and her participation in the study was terminated.

Mean severity score of psoriasis (n=9) at baseline was 7.1 ± 1.1 and after 12 weeks of treatment was 5.0 ± 1.6 ($P \leq .05$) (*Figure 1*). Of the three variables (scale, erythema, thickness) used to generate a psoriasis score, only the degree of thickness at week 12 of treatment was significantly decreased from baseline ($P \leq .05$). The mean extent of involvement decreased from 42% to 32% after 12 weeks of treatment ($P = .09$). Overall, six patients showed improvement ranging from minimal to marked, and three were unchanged (*Table 1*); no patient

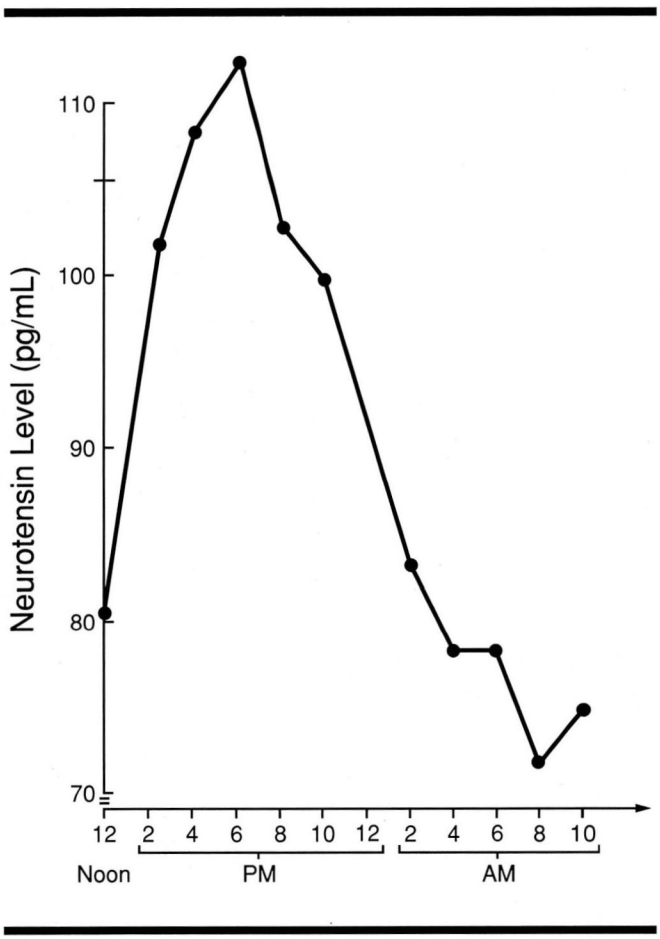

FIGURE 2. Neurotensin levels measured every 2 hours during a 24-hour period in nine psoriatic subjects demonstrate a significant difference over time ($P \leq .05$). In the interest of clarity error bars are not shown. No differences were detected between 0-, 50-, and 100-μg doses of SMS 201-995.

worsened.

Serum substance P and VIP were below the limits of detection of the radioammunoassay (RIA) (<20 pg/mL). A significant circadian rhythm of serum neurotensin levels was observed which was not affected by treatment (*Figure 2*).

The mean stool fat content was 9.1 ± 3.9 mmol/d (2.6 ± 1.1 g/24 hours) at baseline and increased to 45.7 ± 24.6 mmol/d (13.0 ± 7.0 g/24 hours) after one week ($P \leq 0.01$). However, the mean stool fat content tended to normalize as treatment continued, and for the six patients who provided stool specimens 4 weeks after treatment stopped it was 9.8 ± 4.2 mmol/d (2.8 ± 1.2 g/24 hours).

With the exceptions of decreased cholesterol, total protein, hemoglobin, hematocrit, and red blood cell count, and increased fasting glucose, no statistically significant difference between pre-treatment and treatment values was noted for routine blood chemistry, complete blood count, HGH, and SM-C.[14] Differential white blood cell counts and urinalysis were normal and unchanged by treatment.

The most common adverse clinical effects of SMS 201-995 reported in 11 patients were diarrhea (nine patients) and abdominal cramps (seven patients). Both symptoms resolved within 1 week for all but one patient, who had mild diarrhea for 4 weeks. The diarrhea tended to progress to soft stools and then to normal stools. Other adverse effects included bruising at injection sites (five patients), anorexia (four patients), headaches (four patients), Koebnerization of psoriasis (three patients), nausea/vomiting (three patients), and facial flushing (two patients). Subjects lost 3.3 ± 1.3 kg of body weight during the treatment course ($P \leq .05$). Neither adverse clinical effects nor changes in laboratory values were serious enough to discontinue treatment with SMS 201-995 in any patient.

DISCUSSION

Hypotheses concerning the mechanism of action of HGH inhibitors in psoriasis are speculative. Saiag et al[15] demonstrated that psoriatic dermal fibroblasts induced hyperproliferation of normal keratinocytes in a skin equivalent model. They suggested that a mediator produced by fibroblasts resulted in keratinocyte hyperproliferation. Evidence has accumulated to suggest that SM-C may be the factor involved in inducing keratinocyte hyperproliferation.[15–19] Nickoloff et al[20] have indicated that, although plasma SM-C levels are not elevated in psoriasis, SM-C may still exert a local effect on the epidermis. It would be interesting to quantitatively compare psoriatic and normal fibroblast SM-C production.

Substance P, a neuropeptide suggested to play a role in psoriasis,[21] has reportedly stimulated human skin fibroblast proliferation in vitro.[22] Furthermore, neural substance P release is inhibited by SRIF.[23] Unfortunately, in our patients, substance P was not detectable in serum and was not measured in skin.

Epidermal growth factor (EGF) receptors are present on keratinocytes[24] and fibroblasts.[25] Venier et al[26] reported that 11 of 20 patients with severe forms of psoriasis cleared completely after 4 days of continuous intravenous SRIF; plasma EGF levels were significantly

decreased ($P < .01$) after treatment compared to basal levels. EGF was not measured in our study.

The nine of 11 patients who completed 12 weeks of SMS 201-995 treatment had chronic stable plaque psoriasis and had been using fluorinated topical corticosteroids prior to washout. At the end of 12 weeks of therapy with SMS 201-995 six of nine patients had improved, three patients were unchanged, and none worsened. The two patients who did not complete the study had guttate psoriasis and pustular psoriasis, respectively. The former may have improved spontaneously or from prior sun exposure, and the latter definitely flared after methotrexate withdrawal.

Our data and previous determinations of HGH[12] and SM-C[14] levels in psoriatics show no statistically significant elevation of either serum 24-hour pooled HGH or plasma SM-C. Similar to the findings in a study of normal volunteers given 50 μg SMS 201-995 subcutaneously twice a day,[27] our psoriatic patients treated with 50–100 μg SMS 201-995 subcutaneously every 12 hours also did not statistically significantly suppress either 24-hour pooled serum HGH or plasma SM-C. There was, however, a significant improvement in the grading of psoriasis thickness, but not the extent of psoriasis. Therefore, while the mechanism of action of SMS 201-995 in psoriasis is probably different from suppression of serum HGH or plasma SM-C, we cannot rule out that a significant decrease of these hormone levels might have improved psoriasis further.

Many of the systemic side-effects observed or the placebo-effect could have accounted for the modest improvement of psoriasis noted. For example, malabsorption during the first week of treatment resulted in steatorrhea, and there was a significant drop in body weight after 12 weeks. Double-blind placebo-controlled trials must be performed in order to confirm that SMS 201-995 is efficacious in the treatment of psoriasis. In such trials, it will be possible to either control for or eliminate: placebo-effect, observer bias, frequent phlebotomies, inpatient hospitalization, and heparin flushes. However, it still may not be possible to perform a truly blinded investigation of SMS 201-995 in psoriasis because of the high frequency of gastrointestinal disturbances noted in this pilot study.

CONCLUSIONS

Six of nine patients with chronic plaque psoriasis experienced minimal to marked improvement in the subjective evaluation of psoriasis after 12 weeks of treatment with 50 or 100 μg SMS 201-995. Both serum HGH and plasma SM-C levels were not significantly increased prior to treatment nor suppressed during treatment and probably do not play a role in the pathogenesis of psoriasis. SMS 201-995 caused a statistically significant increase in stool fat excretion after one week that tended to normalize during therapy. The frequency of systemic side-effects of the treatment, ie, malabsorption, weight loss, anemia, may have contributed to the modest improvement of psoriasis noted.

Notwithstanding, we believe that the results of this preliminary open-label study justify double-blind, placebo-controlled studies using the same and higher doses of SMS 201-995 to confirm the efficacy of SMS 201-995 in psoriasis.

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