ORIGINAL ARTICLE

Metabolic Effects of a Growth Hormone–Releasing Factor in Patients with HIV

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ABSTRACT

BACKGROUND

Visceral adipose tissue accumulates during antiretroviral therapy in many patients who are infected with the human immunodeficiency virus (HIV); this process is associated with an increased cardiovascular risk. We assessed the use of a growth hormone–releasing factor analogue, tesamorelin, to decrease visceral adiposity.

METHODS

We randomly assigned 412 patients with HIV (86% of whom were men) who had an accumulation of abdominal fat to receive a daily subcutaneous injection of either 2 mg of tesamorelin or placebo for 26 weeks. The primary end point was the percent change from baseline in visceral adipose tissue as shown on computed tomography. Secondary end points included triglyceride levels, the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol, the level of insulin-like growth factor I (IGF-I), and self-assessed body image. Glycemic measures included glucose and insulin levels.

RESULTS

The measure of visceral adipose tissue decreased by 15.2% in the tesamorelin group and increased by 5.0% in the placebo group; the levels of triglycerides decreased by 50 mg per deciliter and increased by 9 mg per deciliter, respectively, and the ratio of total cholesterol to HDL cholesterol decreased by 0.31 and increased by 0.21, respectively ($P<0.001$ for all comparisons). Levels of total cholesterol and HDL cholesterol also improved significantly in the tesamorelin group. Levels of IGF-I increased by 81.0% in the tesamorelin group and decreased by 5.0% in the placebo group ($P<0.001$). Adverse events did not differ significantly between the two study groups, but more patients in the tesamorelin group withdrew from the study because of an adverse event. No significant differences were observed in glycemic measures.

CONCLUSIONS

Daily tesamorelin for 26 weeks decreased visceral fat and improved lipid profiles, effects that might be useful in HIV-infected patients who have treatment-associated central fat accumulation. (ClinicalTrials.gov number, NCT00123253.)

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Abnormalities in metabolism and body composition — including increased visceral adiposity, loss of subcutaneous fat, dyslipidemia, and insulin resistance — are frequent during antiretroviral therapy in patients who are infected with the human immunodeficiency virus (HIV).[1] Therapeutic strategies to decrease visceral adiposity might decrease cardiovascular risk in this population. The use of growth hormone–releasing hormone (GHRH), a hypothalamic peptide that increases the secretion of pituitary growth hormone, has shown a benefit with respect to fat distribution in HIV-infected patients.[2,3] We carried out a multicenter, randomized, placebo-controlled study to assess the efficacy and safety of tesamorelin (Theratechnologies), a synthetic human growth hormone–releasing factor GHRH(1-44) analogue with a trans-3-hexenoyl group added to the N-terminal to increase the half-life over that of native GHRH(1-44).

Methods

Patients

Patients with HIV were recruited at 43 sites between June 2005 and April 2006. Eligibility criteria included the receipt of antiretroviral therapy for at least 8 weeks and an excessive accumulation of abdominal fat, which was defined as a waist circumference of at least 95 cm and a waist-to-hip ratio of at least 0.94 for men and a waist circumference of at least 94 cm and a waist-to-hip ratio of at least 0.88 for women. Other eligibility criteria were similar to those used in our previous phase 2 study of tesamorelin.[3] The use of a stable lipid-lowering regimen within 3 months before randomization and of a stable physiologic testosterone regimen within 6 months before randomization was permitted. Patients who were receiving estrogen or growth hormone or related products within 6 months before randomization or who had a clinical history of pituitary disease were excluded. The study was approved by the institutional review board at each site, and all patients provided written informed consent before screening.

Study Design and Intervention

Patients were randomly assigned in a ratio of 2:1 to receive either 2 mg of tesamorelin or matching placebo, administered by subcutaneous injection daily between 6 a.m. and noon for 26 weeks. Randomization was stratified on the basis of the use of testosterone at baseline and the presence of diet-controlled impaired glucose tolerance or type 2 diabetes mellitus with the use of permuted blocks of 6. Patients and investigators were unaware of assignments to study groups. Assessments of body composition and metabolism were performed at baseline and at weeks 13 and 26. Tesamorelin and matching placebo were distributed as lyophilized powder for reconstitution in sterile water.

The initial 26-week study period was designed to assess the primary efficacy end point, the number of square centimeters of visceral adipose tissue as assessed by computerized tomographic (CT) scanning, and was followed by a 26-week extension phase to evaluate long-term safety. Patients who received tesamorelin in the main phase of the study underwent a second randomization to receive either tesamorelin or placebo in a ratio of 3:1 in the extension phase. Patients receiving placebo in the main phase were assigned to receive tesamorelin in the extension phase. A data and safety monitoring board met every 6 months to review safety data.

Theratechnologies funded and designed the study in consultation with Drs. Grinspoon and Falutz. The statistical analyses were performed by Quintiles Canada, and body-image outcomes were assessed by Phase V. The manuscript was drafted by Dr. Grinspoon. The decision to publish was made by Dr. Grinspoon and Theratechnologies. Dr. Grinspoon vouches for the accuracy and completeness of the data and the analyses.

Assessments

Visceral adipose tissue was determined on CT from a single 5-mm slice obtained between L4 and L5, which has been shown to correlate well with visceral fat volume.[4] Scans were read at a central image reading center (Perceptive Informatics) in a blinded fashion. Lean body mass and the volume of fat in the trunk and limbs were determined from total-body dual-energy x-ray absorptiometry, with results also read centrally. Insulin-like growth factor I (IGF-I) was measured at Esoterix.

Self-perceived body image was determined by a validated questionnaire (Phase V Technologies).[5] Patients rated their "belly size" by comparing their current appearance to their perceived healthy look, with scores ranging from much thinner (–100) to much bigger (+100); they also rated their "belly image distress" about their size, from extremely

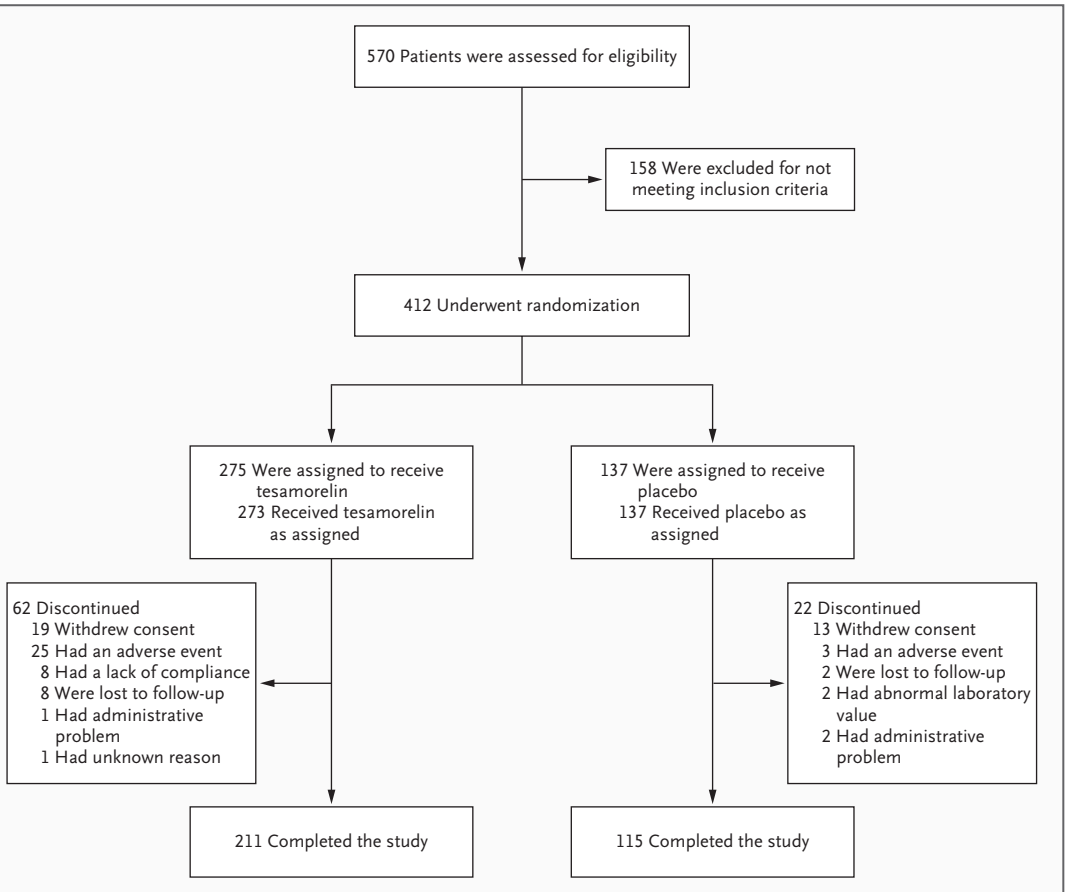

Figure 1. Enrollment and Outcomes.

upsetting and distressing (0) to extremely encouraging (100) and their "belly profile" by choosing from among six silhouettes scored from normal (0) to very dysmorphic (5).

STATISTICAL ANALYSIS

The primary efficacy end point was the percent change in visceral adipose tissue from baseline to week 26. Secondary efficacy end points included the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol, levels of triglycerides and IGF-I, and the patient's perception of body image. The safety end points included adverse events and effects on glucose, insulin, and hematologic and blood chemical analyses.

The efficacy end points were analyzed on the basis of data for patients who had received at least one dose of study drug with the last observation carried forward for those not completing the study. A secondary analysis was performed in patients who completed the study according to the protocol and received a study drug as instructed without a significant protocol violation (per-protocol population). Safety and baseline values are presented for patients who received at least one dose of a study drug. The treatment effect of tesamorelin was estimated according to the difference between placebo and tesamorelin in least-square means from the analysis of covariance.

Supportive analyses were also performed with the inclusion of covariates that were used in the stratification (i.e., testosterone use at baseline and the presence or absence of impaired glucose tolerance or type 2 diabetes mellitus) and the randomization center. The use of nonnucleoside reverse-transcriptase inhibitors was included in supportive models for visceral adipose tissue and lipid end points. The current use of lipid-lowering therapy was included in the model for lipid end points. Fisher's exact test was performed for ad-

Table 1. Demographic and Clinical Characteristics of the Patients.*

Variable	Tesamorelin (N=273)	Placebo (N=137)	P Value
Age (yr)	47.3±7.3	48.3±7.5	0.22
Male:female ratio (%)	86.8:13.2	83.9:16.1	0.43
Race (%)†			0.73
White	76.6	72.3	
Black	13.6	16.1	
Other	9.9	11.7	
Weight (kg)	89.6±14.1	90.0±13.7	0.78
Body-mass index	29.2±4.2	29.2±4.2	0.99
Waist circumference (cm)	104±10	105±9	0.68
Waist-to-hip ratio	1.05±0.06	1.05±0.07	0.72
Viral load (%)			0.90
Undetectable	68.4	70.8	
50–400 copies/ml	22.4	20.4	
>400 copies/ml	9.2	8.8	
CD4 count (cells/mm^3)	616±299	585±284	0.31
Current drug therapy (%)			
Protease inhibitor	55.1	64.2	0.09
Nucleoside reverse-transcriptase inhibitor	97.8	97.8	>0.999
Nonnucleoside reverse-transcriptase inhibitor	53.7	41.6	0.03
Lipodystrophy rating (%)			
Abdominal lipohypertrophy	100	100	NA
Lipoatrophy of face or limbs	72.5	72.3	NA
Fasting glucose (%)			0.86
<110 mg/dl	80.8	81.3	
110–125 mg/dl	16.9	15.7	
>125 mg/dl	2.3	3.0	
Use of testosterone (%)‡	18	18	1.00
Use of lipid-lowering agents (%)§	50	41	0.09

* Plus–minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert the values for glucose to millimoles per liter, multiply by 0.05551. NA denotes not applicable.
† Race was reported by the investigators.
‡ Use of testosterone refers to use at baseline.
§ Use of lipid-lowering agents refers to use either at baseline or during the study.

verse events observed in at least 10% of the patients. All serious adverse events, regardless of frequency, were reported. Baseline comparisons between groups were made by Student's t-test for continuous variables and Fisher's exact test for noncontinuous variables.

The study had a statistical power to detect a difference of 8% between the tesamorelin group and the placebo group in percent change in visceral adipose tissue on the basis of discussions with representatives of the Food and Drug Administration (FDA) to determine the clinical significance of a change in visceral fat, assuming a standard deviation of 18.5%, a power of 90%, a two-sided significance level of 0.05, and a 2:1 distribution ratio of tesamorelin to placebo. The randomization was weighted toward active therapy in order to permit the collection of safety data on the larger number of patients exposed to tesamorelin. An initial dropout rate of 33% was an-

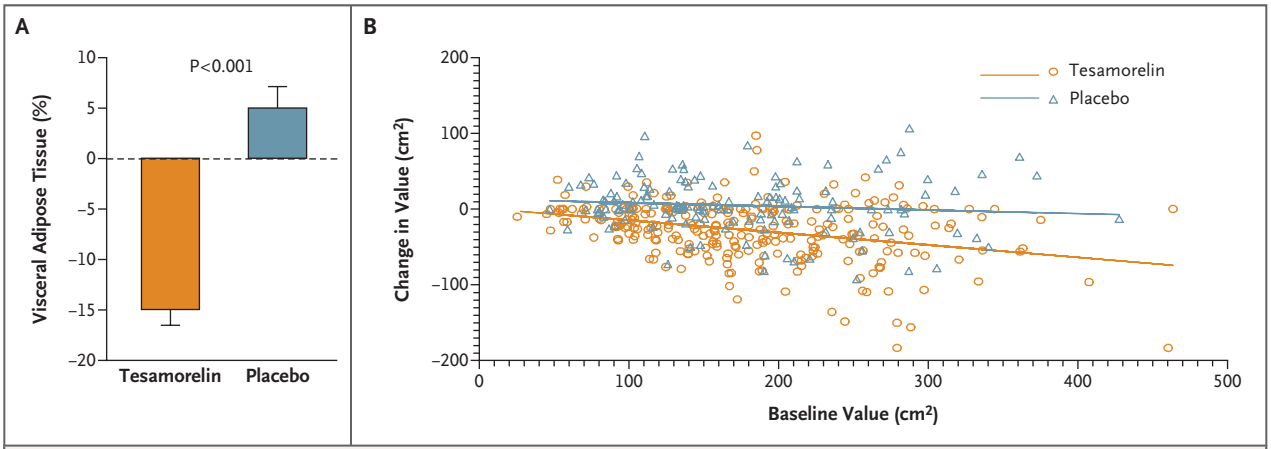

Figure 2. Changes in Visceral Adipose Tissue from Baseline to 26 Weeks.

Panel A shows the mean difference in visceral adipose tissue according to study group; T bars denote the standard error. The P value for the between-group comparison was calculated by analysis of covariance. Panel B shows the relationship of the changes from baseline to 26 weeks in visceral adipose tissue. In the regression equations, the changes from baseline equal 1.24 minus 0.163 times the baseline value in the tesamorelin group and 13.2 minus 0.048 times the baseline value in the placebo group.

ticipated in the study plan. All reported P values are two-sided and were not adjusted for multiple testing.

RESULTS

PATIENTS

Of 412 patients who underwent randomization, 275 were assigned to receive tesamorelin and 137 to receive placebo. The discontinuation rate was 20.5% (22.7% in the tesamorelin group and 16.1% in the placebo group, P=0.12) (Fig. 1). No significant differences in body composition or metabolic or chemical values were seen between the study groups at baseline, although significantly more patients in the tesamorelin group had received nonnucleoside reverse-transcriptase inhibitors (Table 1).

BODY COMPOSITION

The percent change from baseline to week 26 in visceral adipose tissue was significantly greater in the tesamorelin group, which had a decrease of 27.8 cm², as compared with an increase of 5.1 cm² in the placebo group (Fig. 2A). Similar results were observed in the per-protocol population, as defined in the Methods section (data not shown). Results remained highly significant (P<0.001), with adjustment for the use or nonuse of testosterone at baseline, the presence or absence of impaired glucose tolerance or diabetes, sex, center location, and the use or nonuse of nonnucleoside reverse-transcriptase inhibitors. No significant covariate effects or covariate-by-treatment interactions were observed. The change in visceral adipose tissue in the tesamorelin group, as compared with the placebo group, was similar for men and women (data not shown). The change in visceral adipose tissue was larger for patients who had more visceral adipose tissue at baseline (Fig. 2B).

In contrast to changes in visceral adipose tissue, subcutaneous adipose tissue increased by 0.4% in the tesamorelin group and 1.7% in the placebo group. The changes in fat in the limbs of patients were 0.6% and 3.8%, respectively (Table 2).

IGF-I

The changes in IGF-I levels were significant between groups: an increase of 109 ng per milliliter (81.0%) in the tesamorelin group and a decrease of 16 ng per milliliter (5.0%) in the placebo group. When the results were adjusted for age and sex, the mean changes in IGF-I levels represented a standard-deviation score of 2.69±2.51 in the tesamorelin group and −0.39±1.43 in the placebo group.

LIPIDS

The differences in the ratio of total cholesterol to HDL cholesterol and levels of triglycerides, total cholesterol, and HDL cholesterol were significant

Table 2. Changes from Baseline in Body Composition, Lipid Levels, Biochemical Measures, Glycemic Measures, and Immune Function.*

Variable	Baseline		At 26 Weeks		Absolute Difference (95% CI)†	Relative Difference	P Value‡
	Tesamorelin	Placebo	Tesamorelin	Placebo			
			change (percent)		*percent*		
Body composition							
Visceral adipose tissue (cm^2)	178±77	171±77	−27.8±38.6 (−15.2)§	5.1±36.4 (5.0)	−32.9 (−40.7 to −25.0)	−20.2	<0.001
Subcutaneous adipose tissue (cm^2)	231±127	239±133	−3.3±28.8 (0.4)	2.3±29.5 (1.7)	−5.6 (−11.7 to 0.5)	−1.3	0.05
Ratio of visceral to subcutaneous adipose tissue	1.27±1.61	1.18±1.58	−0.25±0.65 (−15.5)§	0.07±0.59 (4.3)	−0.32 (−0.46 to −0.19)	−19.8	<0.001
Trunk fat (kg)	14.9±5.6	15.3±5.8	−1.0±1.9 (−7.3)§	0.4±1.6 (3.6)¶	−1.4 (−1.8 to −1.0)	−11.0	<0.001
Waist circumference (cm)	104±10	105±9	−2.6±4.9 (−2.5)§	−0.8±4.0 (−0.8)¶	−1.8 (−2.8 to −0.9)	−1.7	<0.001
Waist-to-hip ratio	1.05±0.06	1.05±0.07	−0.03±0.05 (−2.6)§	−0.02±0.04 (−1.7)§	−0.01 (−0.02 to 0)	−0.9	0.05
Fat in limbs (kg)	7.1±4.3	7.7±4.7	−0±0.8 (0.6)	0.2±1.0 (3.8)¶	−0.3 (−0.4 to −0.1)	−3.1	0.006
Lean mass (kg)	62.0±10.1	61.4±9.6	1.3±2.4 (2.2)§	−0.2±1.8 (−0.3)	1.6 (1.1 to 2.0)	2.5	<0.001
Body-mass index	29.2±4.2	29.2±4.2	−0.12±1.26 (−0.4)	0.01±1.15 (0.1)	−0.13 (−0.41 to 0.15)	−0.5	0.37
Lipid levels							
Triglycerides (mg/dl)	252±188	234±145	−50±146 (−7.5)§	9±119 (11.6)	−59 (−87.5 to −30.9)	−19.1	<0.001
Cholesterol							
Ratio of total cholesterol to HDL cholesterol	4.50±1.35	4.29±1.24	−0.31±0.98 (−4.7)§	0.21±0.95 (6.1)¶	−0.52 (−0.73 to −0.32)	−10.8	<0.001
Total (mg/dl)	197±44	195±38	−10±33 (−3.3)§	−3±25 (−0.7)	−7 (−14 to −1)	−2.6	0.02
HDL (mg/dl)	47±15	48±15	1±9 (4.1)	−2±10 (−1.0)¶	3 (0.7 to 4.5)	5.1	0.01
Biochemical measures							
Insulin-like growth factor I (ng/ml)	161±59	168±75	109±113 (81.0)§	−16±66 (−5.0)¶	125 (105 to 146)	86.0	<0.001
C-reactive protein (mg/liter)	4.6±9.4	4.4±6.6	−0.4±11.9 (23.9)	0.4±7.9 (75.0)	−0.8 (−3.0 to 1.5)	−51.1	0.54
Adiponectin (μg/ml)	5.3±3.7	5.4±3.2	0.5±2.7 (12.4)¶	−0.1±1.3 (2.4)	0.5 (0.1 to 1.0)	10.0	0.03
Glycemic measures‖							
Glucose (mg/dl)							
Fasting	97±14	99±15	3±13 (3.7)¶	1±15 (1.6)	3 (−1 to 6)	2.1	0.28
At 2 hr	115±41	113±42	1±37 (5.6)	8±44 (15.1)	−7 (−17 to 3)	−9.6	0.17
Insulin (μU/ml)	20±26	18±12	2±29 (35.7)	3±22 (20.9)	−1 (−7 to 5)	14.8	0.93

Immune function							
CD4 count (cells/mm^3)	616±299	585±284	−3±160 (4.5)	0±171 (3.4)	−2 (−40 to 35)	1.0	0.57
Viral load (%)**							0.83
Undetectable	68.4	70.8	66.8	70.2			
50–400 copies/ml	22.4	20.4	23.2	20.2			
>400 copies/ml	9.2	8.8	10.0	9.6			

* Plus–minus values are means ±SD. There were no significant differences between the tesamorelin group and the placebo group at baseline. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for insulin to picomoles per liter, multiply by 6.945.

† The values are for the difference between the changes from baseline in the tesamorelin group and the placebo group.

‡ P values are for the comparison between the changes from baseline in the tesamorelin group and the placebo group.

§ P<0.001 for the within-group comparison between baseline and week 26.

¶ P<0.05 for the within-group comparison between baseline and week 26.

‖ Among patients who had normal glucose values at baseline in the tesamorelin group and the placebo group, the percentages of patients who had increased values at week 26 for fasting glucose (11.1% and 9.7%, respectively) and impaired glucose tolerance (9.5% and 12.5%, respectively) and in whom diabetes was diagnosed (1.0% and 1.9%, respectively) were similar.

** The values are the percentages of patients at baseline and at week 26, plus the P value at week 26.

between the study groups (Table 2). These differences remained significant after adjustment for the use of both lipid-lowering drugs and nonnucleoside reverse-transcriptase inhibitors in a single model. With respect to the ratio of total cholesterol to HDL cholesterol, differences between the tesamorelin group and the placebo group were significantly greater among those who received lipid-lowering therapy than among those who did not receive lipid-lowering therapy (reductions of 0.74 and 0.30, respectively). No other significant treatment interactions were seen for the use of lipid-lowering drugs or nonnucleoside reverse-transcriptase inhibitors with respect to any lipid end points.

BODY IMAGE

Patients' mean changes in scores with respect to "belly image distress" and "belly profile" improved more in the tesamorelin group than in the placebo group, with increases of 11.6±26.9 and 6.2±25.8 (P=0.03), respectively, for distress and decreases of 0.67±1.25 and 0.34±1.25 (P=0.03) for the profile (data not shown). The difference in scores for "belly size" was not significant between the two groups (35.1±55.0 vs. 35.4±55.0, P=0.70).

INFLAMMATORY AND OTHER BIOCHEMICAL MARKERS

Changes in levels of C-reactive protein did not differ significantly between the two groups. However, levels of adiponectin increased significantly more in the tesamorelin group (a relative difference of 10%, P=0.03) (Table 2).

ADHERENCE AND ADVERSE EVENTS

The overall adherence as determined by a count of vials of medication used was 98.9% in the tesamorelin group and 99.5% in the placebo group.

There was no significant difference in levels of fasting blood glucose, 2-hour glucose, and insulin between the study groups after 26 weeks of treatment. Also similar in the two groups were CD4 cell counts and viral loads (Table 2). Clinically significant changes in safety measures were not seen in the tesamorelin group and the placebo group for liver function (alanine transaminase, −4±24 and −2±16 U per liter, respectively), kidney function (with nearly identical measures of creatinine), or blood pressure (diastolic, −2±10 vs. −0±10 mm Hg; and systolic, −2±14 vs. −2±12 mm Hg).

The overall percentages of patients with any adverse event or with a serious adverse event did

not differ between the two groups (Table 3). Four serious adverse events were reported as possibly related to tesamorelin: peripheral neuropathy, febrile diarrhea with dehydration, loss of mobility, and congestive heart failure. A larger percentage of subjects in the tesamorelin group discontinued the study due to an adverse event (Table 3, and Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org). Adverse events resulting in discontinuation were most often related to arthralgias, swelling, and injection-site reactions.

There were no deaths during the randomized phase of the study. Differences in the rate of adverse events that were reported in more than 10% of patients (headache and arthralgias) were not significant between the groups (Table 3).

Among the injection-site reactions, urticaria reactions extending beyond the injection site were observed after 4 to 5 months of treatment in six patients in the tesamorelin group (2.2%) and in no patients in the placebo group; the drug was discontinued in all six patients. In one of these patients, systemic reactions (including nausea, tachycardia, shortness of breath, and sweating) with erythema at previous injection sites developed; these symptoms resolved spontaneously within 3 minutes. All six patients with urticaria tested positive for IgG antibodies against tesamorelin. In addition, IgG antibodies against tesamorelin were detected in 48.6% of patients in the tesamorelin group and 2.7% in the placebo group. The effects of tesamorelin on IGF-I and visceral adipose tissue did not differ significantly in patients with and without antibodies (Table 2 of the Supplementary Appendix).

EXTENSION PHASE

A total of 315 patients entered the extension phase (76.8%) and received at least one dose of a study drug: 204 in the tesamorelin group (74.7%) and 111 in the placebo group (81.0%). The overall dropout rate in the extension phase was 18.7%. Nine serious adverse events were recorded during the extension phase (Table 3), including two deaths in the tesamorelin group, one from complications of tonsillectomy and one from coronary artery disease in a patient with a known history of the condition. None of the serious adverse events were reported by investigators to be related to a study drug in the extension phase. Among patients receiving tesamorelin, 4% in the initial randomized phase had a serious adverse event, and less than 1% had events that were reported to be related to the drug. In the extension phase, 2.6% of patients in the tesamorelin group had a serious adverse event; none of these events were reported to be related to the drug.

DISCUSSION

In this study, tesamorelin, a GHRH(1-44) analogue, significantly decreased visceral adiposity and concomitant dyslipidemia, without worsening overall glucose tolerance, in HIV-infected patients. Such patients who are treated with antiretroviral therapy often have changes in body composition, characterized by an excessive accumulation of visceral fat,[6] a loss of fat in the limbs and in the abdominal subcutaneous tissues,[7] dyslipidemia, glucose intolerance, and insulin resistance,[8] which may increase cardiovascular risk.[9] Such risk is increased with an extended duration of protease-inhibitor therapy, in association with an increased risk of diabetes and dyslipidemia.[10,11] However, interventions to reduce the time that patients receive antiretroviral therapy (such as interruptions in treatment on the basis of CD4 cell counts) may actually worsen cardiovascular disease, as compared with continuous viral suppression.[12] Thus, strategies to improve cardiovascular disease in patients with HIV infection should ideally target risk factors without the compromising of antiretroviral suppression or an interruption in antiretroviral treatment.

Visceral adiposity is associated with cardiovascular disease[13-15] and selective expression of inflammatory adipocytokines.[16,17] Small pilot studies involving patients who are not infected with HIV have suggested that selective reduction of visceral, but not subcutaneous, fat by surgical intervention may be associated with a reduction in cardiovascular risk factors.[18,19] In addition, excess abdominal fat is associated with discomfort and poor self-image[20] and may result in decreased adherence to antiretroviral therapy. Strategies to reduce visceral adiposity have been limited in HIV-infected patients. Insulin-sensitizing agents, lifestyle modification, and resistance training have not shown consistent effects in reducing visceral adiposity or in improving dyslipidemia in HIV-infected patients.[21-30]

Table 3. Adverse Events and Serious Adverse Events.

Event	Tesamorelin (N=273)	Placebo (N=137)	P Value
	percent		
Adverse events			
Any event	82.8	75.2	0.09
Related to treatment	53.8	36.5	0.001
Resulting in study discontinuation	12.1	2.9	0.002
Events reported in >10% of the patients			
Headache	16.1	18.2	0.58
Arthralgias	13.6	10.9	0.53
Events reported in >5% of the patients			
Injection-site bruising	9.2	9.5	
Diarrhea	8.1	9.5	
Peripheral edema	8.4	5.1	
Myalgia	7.7	2.2	
Limb pain	6.2	6.6	
Upper respiratory tract infection	5.5	6.6	
Nasopharyngitis	5.9	5.1	
Hypoesthesia	5.5	0.7	
Rash	5.9	0	
Paresthesia	5.5	2.2	
Fatigue	3.7	6.6	
Sinusitis	4.4	5.8	
Back pain	4.8	7.3	
Dizziness	1.5	6.6	
Injection-site pruritus	5.1	1.5	
Injection-site pain	2.2	5.1	
Serious adverse events*			
Any event	4.0	2.2	0.40
During the randomized phase			
Congestive heart failure	0.4	0	
Diarrhea with dehydration and pyrexia	0.4	0	
Upper respiratory tract infection	0.4	0	
Appendicitis, dehydration, sepsis, and abdominal abscess	0.4	0	
Viral bronchitis	0.4	0	
Arthralgia	0.4	0	
Rectal cancer†	0.4	0	
Decreased mobility	0.4	0	
Basal-cell carcinoma†	0.4	0	
Drug dependence or bipolar disorder	0.4	0	
Peripheral neuropathy	0.4		
Chest pain	0	0.7	
Major depression	0	0.7	
Acute cholecystitis	0	0.7	

* Single episodes of nine serious adverse events were reported during the extension phase of the study. In the tesamorelin group, there was one case of spontaneous abortion, one case of fatal coronary artery disease, one case of pneumonia, one case of intestinal perforation, one case of fatal hemorrhage after tonsillectomy, and two cases of cellulitis. In the placebo group, there was one case of anal cancer (with a previously undisclosed history) and one case of Ludwig's angina.

† This patient was determined to have had a previously undisclosed history of cancer before randomization.

Although growth hormone therapy is most often used to improve bone and muscle mass in patients with growth hormone deficiency caused by a pituitary tumor or exposure to radiation,[31] it is approved by the FDA but not by the European Agency for the Evaluation of Medicinal Products to improve muscle mass in patients with AIDS-related wasting.[32] Recent studies of pharmacologic doses of growth hormone have shown a consistent reduction in visceral adiposity in HIV-infected patients, but highly supraphysiologic levels of IGF-I and symptoms of growth hormone excess have occurred.[33,34]

The effects of tesamorelin appear to be highly specific for the visceral-fat compartment, with relatively little effect on subcutaneous fat or fat in limbs. Our study showed an estimated 1.0-kg selective loss in visceral fat after 6 months of treatment. As a comparison, a pilot study of surgical omentectomy of visceral fat in obese patients without HIV infection resulted in a net loss of 0.6 kg in visceral fat during a 24-month period and selective reduction in measures of cardiovascular risk.[19] Among men without HIV infection, weight loss and exercise can reduce visceral fat by 1.1 kg but also reduce subcutaneous fat.[35] However, patients in our study were not simply obese but also had a mixed pattern of lipodystrophy, with the majority having peripheral lipoatrophy in addition to abdominal obesity at baseline. The preferential reduction in visceral adipose tissue is important in this population, given their peripheral lipoatrophy. The reduction in visceral adiposity was associated with the degree of baseline visceral adiposity, suggesting that larger effects might be seen among patients with more accumulation of visceral fat. Patients receiving tesamorelin reported having a reduction in distress related to abdominal size, which might improve the quality of life and adherence to antiretroviral treatment.

The numbers of overall and serious adverse events were not significantly higher among patients receiving tesamorelin than among those receiving placebo, but were generally high in the two study groups, which is consistent with underlying medical illness. However, more tesamorelin-treated patients had adverse events that led to study discontinuation. The percentage of patients reporting symptoms of growth hormone excess — including arthralgias, peripheral edema, and myalgias — was lower than in previous large trials of growth hormone in HIV-infected patients.[33,34] However, antibodies developed in almost 50% of patients receiving tesamorelin. Our study was of short duration, and the long-term side effects (including the presence of antibodies) and benefits (particularly in terms of cardiovascular outcome) remain unknown. Tesamorelin is not FDA-approved and is undergoing testing in phase 3 studies.

The use of nonnucleoside reverse-transcriptase inhibitors was more frequent among the tesamorelin-treated patients and may have influenced body composition and lipid end points.[36] However, differences in end points for visceral fat and lipids remained significant after controlling for the use of nonnucleoside reverse-transcriptase inhibitors. The numbers of female patients were limited, but similar effects of tesamorelin were seen within each sex. Dropout rates did not differ significantly between the two groups and probably did not affect the results. Further studies to determine the long-term safety of tesamorelin are needed.

In summary, treatment with tesamorelin during a 6-month period resulted in a highly significant and selective reduction in visceral fat, with simultaneous improvements in dyslipidemia, without significant adverse effects on glycemic measures. Tesamorelin might be useful for the treatment of HIV-infected patients who have an increase in abdominal girth and dyslipidemia in the context of receiving antiretroviral therapy.

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APPENDIX

In addition to the authors, the following investigators participated in the study: *Clinique Médicale du Quartier Latin, Montreal* — P. Côté; *Montreal General Hospital, Montreal* — J. Falutz; *St. Paul's Hospital, Vancouver, BC, Canada* — J. Montaner; *Southern Alberta HIV Clinic, Calgary, AB, Canada* — J.M. Gill; *HIV Care Program, Windsor Regional Hospital, Windsor, ON, Canada* — C. Quan; *Sunnybrook and Women's College Health Sciences Centre, Toronto* — A. Rachlis; *New York University Medical Center, New York* — J. Aberg; *St. Luke's–Roosevelt Hospital, New York* — J. Albu; *Infectious Disease Physicians, Annandale, VA* — S. Ambardar; *University of Texas Medical School of Houston, Houston* — R. Arduino; *Northstar Healthcare, Chicago* — D. Berger; *Dallas Veterans Affairs Medical Center, Dallas* — R. Bedimo; *Central Texas Clinical Research, Austin, TX* — C. Brinson; *AIDS Research Alliance, West Hollywood, CA* — S. Brown; *Johns Hopkins University School of Medicine, Baltimore* — T. Brown; *Center for Special Immunology, Fountain Valley, CA* — P. Cimoch; *Fanno Creek Clinic, Portland, OR* — G. Coodley; *Community Research Initiative of New England, Boston* — C. Cohen; *UCLA School of Medicine, Los Angeles* — J. Currier; *University of Maryland Institute of Human Virology, Baltimore* — C. Davis; *Orlando Immunology Center, Orlando, FL* — E. DeJesus; *Indiana University Department of Medicine, Indianapolis* — M. Dube; *AIDS Community Research Initiative of America, New York* — J. Ernst; *Kaiser Permanente, San Francisco* — J.W. Fessel; *University of Cincinnati Medical Center, Cincinnati* — J. Feinberg; *Bach & Godofsky, Bradenton, FL* — E. Godofsky; *Massachusetts General Hospital, Boston* — S. Grinspoon; *Hennepin County Medical Center, Minneapolis* — K. Henry; *Rush University Medical Center, Chicago* — H. Kessler; *Body Positive, Phoenix, AZ* — R. Myers; *University of California San Diego Medical Center, San Diego* — D. Lee; *Treasure Coast Infectious Disease Consultants, Vero Beach, FL* — G. Pierone; *Capital Medical Associates, Washington, DC* — B. Rashbaum; *Fort Lauderdale, FL* — G.J. Richmond; *Care Resource, Miami* — S. Santiago; *Swedish Medical Center, Seattle* — P. Shalit; *Community Research Initiative of New England, Springfield, MA* — D. Skiest; *Drexel University College of Medicine, Philadelphia* — P. Sklar; *Infectious Disease, Palms Springs, CA* — M. Somero; *AIDS Research Consortium of Atlanta, Atlanta* — M. Thompson; *St. Vincent's Hospital and Medical Center, New York* — A. Urbina; *Infectious Diseases Associates, Sarasota, FL* — W. Vega; *Tufts New England Medical Center, Boston* — C. Wanke.

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