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Effects of Recombinant Human Growth Hormone (r-hGH) on Fat Depletion and Plasma Lipids in HIV-1 Infected Patients with Lipodystrophy - A Randomised, Open-label Study

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1. JW Goethe University, Department of Infectious Disease, Frankfurt, Germany
2. JW Goethe University, Department of Radiology, Frankfurt, Germany
3. Internistisches Facharzt Zentrum Stresemannalle (IFS), Frankfurt, Germany
4. Gemeinschaftspraxis Grueneburgweg, Frankfurt, Germany
5. Medizinische Poliklinik, Klinikum der LMU Munich, Germany

Markus Bickel 1, Stefan Zangos 2, Volkmar Jacobi 2, Gabi Knecht 3, Thomas Lutz 4, Frank Goebel 5, Schlomo Staszewski 1 and Stephan Klauke 3

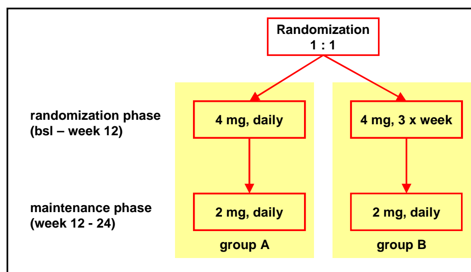
Introduction

The HIV associated lipodystrophy syndrome has become a major challenge in the treatment of HIV disease. The syndrome involves intraabdominal (visceral) adiposity, development of antero- and dorsocervical fat pads (buffalo hump), breast enlargement and symmetric lipomatosis as signs of fat accumulation as well as loss of subcutaneous fat of the face, limps, trunk and the buttock on the other hand (1 – 7). Visceral adiposity, one of the hallmarks of HIV associated lipodystrophy syndrome, is a known independent risk factor for insulin resistance and cardiovascular complications in HIV negative subjects (8 -10) and therefore became one of the major concerns for long term complications of highly active antiretroviral therapy (HAART). Recent studies suggest an increase of cardio- and cerebrovascular events associated with increasing duration of HAART; although some results are controversial (11 – 15).
HIV-infected and uninfected patients with visceral obesity were shown to have a blunted growth hormone (GH) secretion and low serum insulin-like growth factor-I (IGF-1) concentrations (16, 17). Taken these findings together with the beneficial effects on fat maldistribution in GH deficient and abdominal obese patients treated with recombinant human growth hormone (r-hGH) (18, 19), several trials in HIV-1 infected patients were undertaken also demonstrating beneficial effects of r-hGH and of GH releasing hormone in patients suffering from visceral and dorsocervical fat accumulation (20 – 27). The optimal dose and duration of r-hGH treatment is to be determined. Concerns about a reduction of subcutaneous fat, especially in the facial region, and therefore a worsening of the fat loss were raised.

Table 1: Baseline demographic and HIV treatment characteristics.

Demographics	4 mg rhGH daily	4 mg rhGH three times weekly
number of patients enrolled	**12**	**14**
sex	11 m, 1 f	14 m
age	45.8 ±7.1	43,9±8.7
race	11 w, 1 b	14 w
HIV and treatment history		
MSM (%)	75.0	78.6
duration of HIV-1 infection (years)	11.1 ±4.2	13.3 ±3.8
CD4 cell count (cells/µl)	546 ± 316	476 ± 219
HIV RNA PCR < 400 copies/ml (%)	100	93
HIV RNA PCR < 50 copies/ml (%)	83	86
duration of lipodystrophy (years)	3.2 ±1.9	2.3 ±1.1
Antiretroviral treatment		
No. antiretroviral therapies (min-max)	9 (3 – 18)	9 (4 – 22)
Previous mono-NRTI treatment (%)	50	64
Previous dual-NRTI treatment (%)	83	93
cumulative duration of ART (years)	6.6 ±1.5	7.4 ±1.3
Current NRTI, No. (%)	10 (83)	11 (78.6)
Current NNRTI, No. (%)	8 (66.6)	5 (35.7)
Current PI, No. (%)	4 (33.3)	11 (78.6)

Figure 1 • study flow chart



Methods

Adult HIV-1 infected patients with clinical symptoms of fat accumulation on stable HAART were eligible to take part in this pilot study and were randomized as shown in figure 1. Patients were allowed to switch from 4 mg daily to 4 mg three times a week in group A or to half the dose in group B respectively in the case of drug related adverse events (AE). At major study visits (baseline, week 12 and 24) fasting metabolic parameters (incl. OGTT), WHR, body composition (BIA) and fat distribution (MRI) were measured. Patients with known malignancies, active opportunistic infections, uncontrolled hypertension, carpal tunnel syndrome or diabetes mellitus were excluded.

Table 2 • mean change of anthropometric and body composition parameters

	baseline	week 12	week 24
	mean ± SD	mean ± SD (% change to bsl)	mean ± SD (% change to bsl)
Magnet resonance tomography			
VAT (cm2)			
A	103 ± 77	68 ± 58 (-27)	54 ± 39 (-42)
B	139 ± 56	96 ± 55 (-29)	83 ± 39 (-38)
SAT (cm2)			
A	209 ± 93	169 ± 105 (-13)	138 ± 54 (-17)
B	171 ± 75	155 ± 87 (-13)	155 ± 85 (-13)
facial fat (cm2)			
A	16.4 ± 6.8	12.2 ± 6.4 (-20.1)	12.0 ± 6.4 (-19.5)
B	13.6 ± 3.6	10.7 ± 4.4 (-19.1)	10.9 ± 4.5 (-17.4)
right mid thigh fat (cm2)			
A	62.7 ± 27.3	46.6 ± 34.5 (-14.2)	50.3 ± 31.3 (-21.2)
B	41.6 ± 34.6	36.2 ± 29.9 (-12.7)	46.6 ± 32.6 (9.9)
Anthropometric measurements			
waist circumference (cm)			
A	98.8 ± 8.4	90.9 ± 9.0 (-5.7)	86.8 ± 6.7 (-8,2)
B	99.1 ± 7.7	93.5 ± 8.0 (-5.1)	91.6 ± 8.7 (-6.5)
hip circumference (cm)			
A	94.0 ± 8.3	88.6 ± 5.8 (-3.1)	86.4 ± 4.2 (-3.5)
B	92.2 ± 6.5	91.3 ± 6.4 (-0.3)	89 ± 6.9 (-1.5)
right leg circumference (cm)			
A	53.5 ± 5.3	55.8 ± 4.5 (-3.2)	54.1 ± 6.1 (0)
B	52.8 ± 4.8	53.4 ± 5.1 (-0.6)	54.1 ± 4.5 (1.7)
Bioelectric impedance analysis			
total body fat (kg)			
A	17.9 ± 4.8	9.4 ± 3.8 (-41.3)	9.7 ± 3.2 (-36.9)
B	16.9 ± 5.2	12.6 ± 4.3 (-21.3)	11.7 ± 5.2 (-26.0)
body cell mass (kg)			
A	35.9 ± 6.0	38.5 ± 7.0 (9.5)	37.4 ± 7.6 (7.0)
B	34.7 ± 4.9	35.8 ± 5.3 (3.5)	36.0 ± 6.1 (5.8)
Fasting metabolic parameters			
triglycerides (mg/dl)			
A	243 ± 139	232 ± 106 (-16)	278 ± 223 (+3)
B	336 ± 180	312 ± 144 (-10)	310 ± 140 (-16)
total cholesterol (mg/dl)			
A	216 ± 50	195 ± 35 (-15)	216 ± 50 (-7.6)
B	206 ± 52	207 ± 49 (-4)	214 ± 47 (-0.4)
HDL cholesterol (mg/dl)			
A	47 ± 15	49 ± 11 (+11)	53 ± 10 (+15.2)
B	39 ± 12	44 ± 7 (+6)	41 ± 8 (-1)
LDL cholesterol (mg/dl)			
A	128 ± 34	104 ± 13 (-23)	121 ± 15 (-11.5)
B	120 ± 43	122 ± 41 (-4)	124 ± 49 (-0.6)
AST (SGOT) (U/l)			
A	53 ± 30	41 ± 20 (-17)	40 ± 12 (-23)
B	41 ± 20	33 ± 11 (-13)	32 ± 6 (-18)
ALT (SGPT) (U/l)			
A	75 ± 71	51 ± 56 (-31)	39 ± 18 (-52)
B	52 ± 34	50 ± 38 (-26)	29 ± 10 (-40)
glucose (mg/dl)			
A	95 ± 19	93 ± 15 (2)	93 ± 9 (4)
B	97 ± 15	98 ± 14 (1.6)	97 ± 15 (0.2)

Results

26 subjects (96% white, 96% male, mean age 44.8 y, mean duration of HIV 12.3 y) were included. Four patients (3 of group A) permanently stopped the study drug until week 12. Three patients (all of group A) reduced the dose of the study drug until week 12, as defined by the study protocol, because of non serious AE´s. The AE´s resolved and all three patients completed the 24 study period. During the maintenance phase (between week 12 and week 24) two more patients (one of each group) discontinued due to adverse events. Overall AE´s probably related to r-hGH were more often reported in group A (67 % of the subject) compared to group B (29 %). Four patients in group A experienced severe side effects possibly related to study drug (dyspepsia, peripheral oedema, hyperglycaemia and pain of the extremity), whereas none were reported for group B.
Overall VAT, waist- and hip-circumference were significantly reduced after 12 and 24 weeks of treatment compared to baseline ($p<0.01$ for all parameters). No significant difference was found between group A and B. Over 12 weeks treatment, total abdominal adipose tissue was reduced by 60 cm^2 overall, while facial fat was reduced by 3.3 cm^2 and 2.6 cm^2 in A and B respectively ($p=0.960$, non significant dose comparison, NSDC). Over the 24 week study period, a total reduction of facial fat by 3.2 and 2.4 cm^2 was observed in A and B respectively ($p=0.911$,NSDC). Thigh fat, assessed in a small subset of patients, was reduced by 8.9 cm^2 and 5.3 cm^2 over 12 weeks ($p=0.8$, NSDC) and by 13.2 and 4.1 cm^2 over 24 weeks ($p=0.316$, NSDC) in A and B respectively, while leg circumference did not change. Total cholesterol was reduced by 31.3 and 8.1 mg/dl over 12 weeks in A and B respectively ($p=0.046$, significant dose comparison, SDC) and maintained over 24 weeks. There was a greater reduction in LDL in A than in B (28.9 vs 4.2 mg/dl at week 12 and 14.7 mg/dl vs 0.7 mg/dl at week 24) although not statistically significant different. There was a greater increase in HDL in A than in B (4.9 vs 2.4 mg/dl at week 12, NSDC and 7.1 mg/dl vs a reduction by 0.4 mg/dl at week 24, $p=0.030$, SDC). 4 patients in group A and 2 patients in group B discontinued due to AEs. No drug-related serious AE or newly onset diabetes occurred. Baseline and changes of primary and secondary endpoints are summarized in table 2.

Figure 2 • MRI of the abdomen, face and mid thigh level (day 0, w12 and 24)

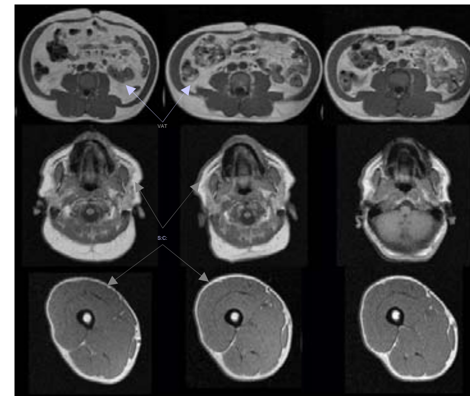
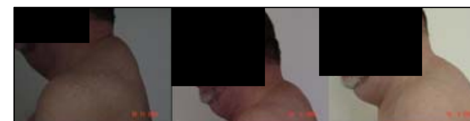


Figure 2 and 3 show the MRI scans and photos of one patient who received 4 mg of r-hGH daily over 12 weeks followed by 2 mg daily. Arrows indicate the different regions of fat assessed. Compared to the large reduction of visceral adipose tissue (VAT) of the abdomen and the dorsocervical region (buffalo hump), the reduction of peripheral subcutaneous fat (S.C) of the face and thigh is relatively small.

Figure 3 • photos of a patient with buffalo hump (day 0, w12 and 24)



Discussion

Patients with any signs of fat accumulation were eligible to take part in this study, therefore patients with dorsocervical fat accumulation and symmetric lipomatosis were included besides having normal amounts of visceral adipose tissue and thereby leading to the wide SD of the parameters. Furthermore patients in group B more often received a PI based HAART, had a significantly higher VAT, less amounts of subcutaneous fat besides having a lower BMI reflecting a more severe lipodystrophy at baseline. This together with the relatively small number of patients and the wide standard deviation (SD) may explain the similar results obtained in terms of VAT reduction in the two groups. Kotler et al. have shown an inverse correlation between the loss of visceral fat using r-hGH and the amount of VAT before starting suggesting a more pronounced effect in patients with more severe lipodystrophy (23). The lower dose was generally better tolerated leading to a smaller number of adverse events, dose reductions and treatment discontinuations.
Interestingly the reduction of subcutaneous fat of the abdomen, legs and the face was relatively small compared to the reduction of visceral fat during the first 12 weeks (12 – 20 %). During the maintenance phase using 2 mg per day in both groups a further reduction of VAT by approximately 10 % was achieved in both groups while there was again a small reduction of subcutaneous fat in group A, but no further depletion in group B. Improvement of total-, LDL- and HDL- cholesterol was significantly more in patients A than B confirming earlier findings.

Conclusions

This study confirms previous reports that r-hGH effectively reduces VAT in lipodystrophic HIV+ patients, however optimal dose must be determined in large, randomized trials. Importantly, this exploratory study shows that facial and thigh peripheral sc fat reductions following 12 weeks treatment did not differ between the two doses of r-hGH, and no further reduction was observed during maintenance therapy. Moreover, significant dose related improvements in total and HDL cholesterol levels were observed.

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