Double-blind, randomized, placebo-controlled phase III trial of oxymetholone for the treatment of HIV-wasting

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ABSTRACT

Background: Despite highly active antiretroviral therapy (HAART), chronic involuntary weight loss of lean body mass (LBM) and body cell mass (BCM). still remains a serious problem in the care of HIV patients. Previous studies have been performed with androgen replacement therapy or treatment with recombinant growth hormone (rGH) showing partial restoration of LBM, but these treatments have largely not been assessed in eugonadal individuals.

Study Design: Double-blind, randomized, placebo-controlled trial of 89 HIV-positive women and men with wasting assigned to the anabolic steroid oxymetholone (50 mg BID or TID) or placebo for 16 weeks followed by open-label treatment.

Results: Oxymetholone led to a significant weight gain of 3.0 ± 0.5 and 3.5 ± 0.7 kg in the TID and BID groups, respectively ($p<0.05$ for each treatment versus placebo), while individuals in the placebo group gained an average of 1.0 ± 0.7 kg. Body cell mass increased in the oxymetholone BID group (3.8 ± 0.4 kg; $p<0.0001$) and in the oxymetholone TID group (2.1 ± 0.6 kg; $p<0.005$), corresponding to 12.4% and 7.4% of baseline BCM, respectively. The most important adverse event was liver-associated toxicity. Overall, 35% of patients in the TID, 27% of patients in the BID oxymetholone group and no patients the placebo group had a greater than 5 times baseline increase for ALT during the double-blind phase of the study.

Conclusions: Oxymetholone can be considered an effective anabolic steroid in eugonadal male and female patients with AIDS-associated wasting. The BID (100 mg/day) regimen appeared to be equally effective to the TID (150 mg/day) regimen in terms of weight gain, LBM and BCM and was associated with less, but still significant liver toxicity.

INTRODUCTION

While wasting was one of the early manifestations of symptomatic AIDS, its prevalence has considerably decreased in the era of highly active antiretroviral therapy (HAART). However, chronic involuntary weight loss still remains a serious problem even with HAART

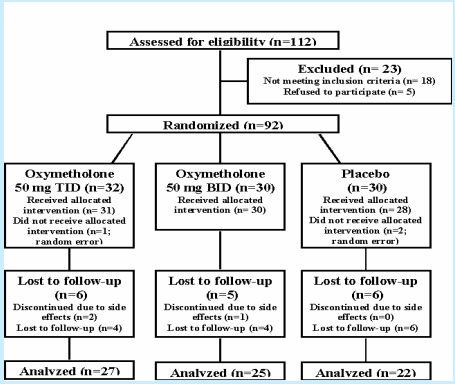
Anabolic steroids are known to cause protein anabolism leading to an increase in LBM. Oxymetholone, 17-a-methyl-2-hydroxymethylene dihydrotestosterone, has an anabolic potency compared to its androgenic effect of 8.75:1 relative to methyltestosterone. Based on our earlier findings with oxymetholone suggesting a significant weight gain in advanced HIV-patients, we performed a double-blind, randomized, placebo-controlled trial in 89 women and men with HIV-infection.

Materials and Methods

Our study was a double-blind, randomized, placebo-controlled trial to compare two different doses of oral oxymetholone with placebo long-term (Figure 1).

89 patients (79 men and 10 women; 69 homo-/bisexual; 12 IVDUs; 7 heterosexual contact; 1 transfusion recipient) were enrolled between 1998 and 2000. The protocol was approved by the local IRB, and informed consent was obtained for all procedures.

FIGURE 1. Study Design.



Inclusion Criteria

1. HIV-seropositive

2. had experienced at least a 5% weight loss during the preceding 6 months or had a sustained weight loss of 10% below ideal body weight according to Broca that occurred up to 12 months prior to screening

3. were on stable HAART (> 3 months) with at least 3 antiretroviral drugs, including one protease inhibitor

4. had sufficient liver function

5. were not currently participating in progressive resistance or aerobic exercise

6. had a negative pregnancy test, if they were of childbearing age;

7. had an unremarkable prostate on PSA (< 4 mg/dl) and clinical examination.

Statistical Analysis

All computations for statistical analyses were performed using SAS version 6.12. All hypothesis testing used two-sided tests performed at a 0.05 level of statistical significance.

Results

Patient details

Eighty-nine patients were randomized into the double-blind phase of the study. Unfortunately, randomization led to an uneven distribution of women across groups and consequently to lower LBM and BCM in the placebo group (Table 1).

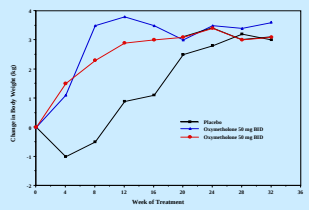
	Oxymetholone 50 mg TID n=31	Oxymetholone 50 mg BID n=30	Placebo n=28
Age (yrs) Mean (Range)	37.3 (26-59)	41.4 (26-64)	38.2 (26-67)
Sex: Female / Male	4 (13%) / 27 (87%)	2 (7%) / 28 (93%)	4 (14%) / 24 (86%)
Race: Black/Latino / Caucasian	2 (6%) / 29 (94%)	2 (6%) / 28 (93%)	2 (8%) / 26 (93%)
CD4 cells (/µl)	484 ±245	417 ±175	529 ±417
h-DNA (Eq/ml)	33884± 105894	19294 ± 42586	14293 ± 43723
Weight (kg)	65.6 ±10.4	64.8 ±9.0	60.5 ±8.0
Body Cell Mass* (kg)	30.2 ±6.2	30.1±4.6	25.0 ±4.2
Lean Body Mass** (kg)	56.9 ±9.7	56.9 ±6.9	49.6 ±7.1
Body Mass Index[&] (kg/m²)	20.9 ±2.4	20.8 ±1.7	19.4 ±1.6

Significant differences (one-way ANOVA) for BCM (*p= 0.0029), LBM (p= 0.0072), and BMI ([&]p= 0.0047). The difference in body weight across treatment groups was not significant at baseline (p= 0.0866).**

Mean Change of Body Weight

The onset of weight gain was observed after an average of 2 weeks after the start of therapy (Figure 2). Body weight gain plateaued between week 8 and 12. Upon switching the placebo patients to oxymetholone 50 mg BID, this patient group experienced similar body weight gain as patients who were initially treated with oxymetholone.

FIGURE 2. Weight change (kg) over time



Body Composition

Analysis of body composition is shown for the individual time points (Table 2).

TABLE 2 Body composition changes over the course of the study

		Oxymetholone 50 mg TID n=27	Oxymetholone 50 mg BID n=25	Placebo n= 22
Body weight[1]	Baseline	66.4 ± 10.4	66.1 ± 9.0	60.9 ± 8.0
	Week 16	69.4 ± 9.9	69.6 ± 10.2	61.9 ± 8.4
	Change	3.0* ± 0.5	3.5* ± 0.7	1.0 ± 0.7
BMI[1]	Baseline	21.0 ± 2.5	21.0 ± 1.8	19.4 ± 1.7
	Week 16	22.0 ± 2.4	22.0 ± 2.2	19.8 ± 2.1
	Change	1.0* ± 0.2	1.0* ± 0.2	0.4 ± 0.2
LBM[1]	Baseline	54.3 ± 9.6	57.0 ± 6.6	48.3 ± 7.1
	Week 16	56.1 ± 8.2	59.9 ± 7.6	48.8 ± 7.3
	Change	1.8** ± 0.8	2.9* ± 0.54	0.5 ± 0.8
BCM[1]	Baseline	28.3 ± 5.4	30.5 ± 4.2	24.2 ± 3.5
	Week 16	30.4 ± 4.9	34.3 ± 5.1	24.9 ± 4.4
	Change	2.1* ± 0.6	3.8* ± 0.4	0.7 ± 0.5
Body fat[1]	Baseline	11.8 ± 6.4	9.7 ± 3.6	9.5 ± 3.1
	Week 16	11.7 ± 5.0	10.0 ± 5.2	9.8 ± 3.9
	Change	0.0 ± 0.7	0.3 ± 0.7	0.4 ± 0.6
Body water[1]	Baseline	39.7 ± 7.0	41.7 ± 4.8	35.4 ± 4.5
	Week 16	41.1 ± 6.0	44.0 ± 5.5	35.8 ± 5.4
	Change	1.3 ± 0.6	2.3* ± 0.4	0.4 ± 0.6
ECM/BCM	Baseline	0.92 ± 0.1	0.88 ± 0.09	0.99 ± 0.14
	Week 16	0.84 ± 0.09	0.76 ± 0.07	0.98 ± 0.14
	Change	-0.08** ± 0.03	-0.12* ± 0.01	-0.01 ± 0.01

* (p-0.0001). ** (p<0.05). [&] (p<0.005).

Adverse events

Side effects are shown in Table 3. Note the significant liver toxicity.

TABLE 3 Adverse events

Double-Blind Phase Side Effects	50 mg TID N=31		50 mg BID N=30		Placebo N=28	
	N	%	N	%	N	%
Non-liver associated	30	97	33	110[&]	24	86
Abnormal liver function[1]	11	35	8	27	2	7
Open-Label Phase Side Effects	**50 mg TID* N=25**		**50 mg BID* N=25**		**Placebo* N=22**	
	N	%	N	%	N	%
Non-liver associated	14	58	15	60	8	36
Abnormal liver function[1]	7	28	4	16	3	14

[1] Abnormal liver function during the 16-week study includes elevated liver enzymes, jaundice, and hepatomegaly.

An intercurrent hepatitis A (n=1; oxymetholone BID group), cholelithiasis (n=1; placebo) and concurrent alcohol abuse (n=2; one each in the oxymetholone TID and BID group, respectively) were the probable causes of liver toxicity in 4 patients. Most of the non liver-associated side effects were not considered related to the study drug.

Serum Gonadal Hormone Concentrations

All patients in our trial were eugonadal at the beginning of the trial (Table 4). Total serum testosterone significantly declined in patients receiving oxymetholone (Table 4).

TABLE 4 Gonadal hormones during the study

		Oxymetholone 50 mg TID n= 27	Oxymetholone 50 mg BID n= 25	Placebo n= 22
Testosterone Males	Baseline	7.1 ± 2.5	5.9 ± 2.6	7.0 ± 3.6
	Week 16	3.0 ± 2.0	1.7 ± 0.9	7.2 ± 3.4
	Change	-4.2* ± 0.8	-4.2* ± 0.6	0.2 ± 0.8
LH Males	Baseline	5.6 ± 2.6	4.9 ± 3.4	7.9 ± 7.6
	Week 16	2.7 ± 1.8	1.7 ± 1.8	6.9 ± 5.9
	Change	-2.9[$] ± 0.6	-3.2[$] ± 0.7	-1.0 ± 1.3
FSH Males	Baseline	7.2 ± 2.9	6.0 ± 4.9	10.5 ± 10.0
	Week 16	4.4 ± 2.6	2.2 ± 1.9	11.2 ± 9.9
	Change	-2.8* ± 0.6	-3.8** ± 1.0	0.7 ± 1.2

* (p<0.0001). [$] (p<0.0005). ** (p<0.001).

Total testosterone (normal range for men: 1.7-8.9 ng/ml; women: 0.0-1.3 ng/ml);

LH (normal range: 0.4-5.7 IU/l; FSH (normal range: 1.1-13.5 IU/l).

DISCUSSION

Oxymetholone equaled or surpassed the gains in weight and LBM observed with cytokine inhibitors, nutritional supplements and rGH, its side effect profile was different. The suppression of pituitary gonadotropins, that regulate the endogenous testosterone, occurs by a negative feed back loop and represents a well-known side effect of anabolic steroids.

When other first-line therapies such as optimizing nutritional status and gonadal function or the use of exercise have failed, oxymetholone can be considered an effective anabolic steroid in male and female patients with AIDS wasting, promoting significant gains in LBM and BCM.

Reference:

UR Hengge, K Stocks, H Wiebler, S Faulkner, S Esser, C Lorenz, W Jentzen, D Hengge, M Goos, R Dudley, G Ringham (2003). Double-blind, randomized, placebo-controlled phase III trial of oxymetholone for the treatment of HIV-wasting. AIDS 17: 699-710