Evaluation of the Effects of Oxandrolone on Malnourished HIV-Positive Pediatric Patients

Sarah Fox-Wheeler, MSN*; Linda Heller, MS, RD, CSP*; Cathleen M. Salata, RN*; Francine Kaufman, MD‡; M. Louisa Loro, MD§; Vincente Gilsanz, MD§; Michael Haight, MD‖; Gwenn C. Umman, RN, PhD¶; Norman Barton, MD, PhD#; and Joseph A. Church, MD*

ABSTRACT. *Objective.* **To determine the safety and efficacy of anabolic therapy to prevent or reverse wasting and malnutrition in human immunodeficiency virus (HIV)-infected pediatric patients. The anabolic steroid, oxandrolone, was evaluated because of its safe and effective use in other pediatric conditions.**

Methods. **Nine HIV-positive children who were malnourished or at risk for malnutrition (4 females, 5 males; 4–14 years of age) took oxandrolone for 3 months (.1 mg/kg/day orally). Quantitative HIV ribonucleic acid polymerase chain reaction and CD4+ T-cell levels, complete blood cell count (CBC) and chemistry profile, endocrinologic studies, resting energy expenditure, respiratory quotient, nutritional measures, body composition assessment with quantitative computed tomography, and skinfold body composition measurements were determined before treatment, during treatment (3 months), and for 3 months after treatment. Statistical analyses were completed using the Friedman two-way analysis of variance and Spearman correlation tests.**

Results. **No adverse clinical or laboratory events or changes in Tanner staging or virilization occurred. Quantitative HIV ribonucleic acid polymerase chain reaction and CD4+ T-cell levels did not change significantly. Insulin-like growth factor 1 increased, suggesting an anabolic effect of treatment. The rate of weight gain increased during treatment and was maintained after treatment. Linear growth continued and was maintained throughout treatment, whereas bone age did not increase significantly. Anthropometric assessments indicated an increase in muscle mass and a decrease in fat while patients were on treatment, and a mild decrease of muscle and increased fat posttreatment. Likewise, computed tomography scan results demonstrated similar changes in muscle mass. Resting energy expenditure and respiratory quotient remained stable throughout treatment and follow-up. No significant changes were seen in the quality of life questionnaire.**

Conclusions. **Treatment with oxandrolone for 3 months in HIV-infected children was well-tolerated, safe, and associated with markers of anabolism. The latter effect was maintained partially for 3 months after discontinuation of a 3-month course of therapy. Additional studies are needed to assess the potential benefits and risks of a longer course of therapy or a higher dose of oxandrolone in HIV-infected children.** *Pediatrics* **1999; 104(6). URL: http://www.pediatrics.org/cgi/content/full/104/6/e73;** ***anabolic steroids, oxandrolone, malnutrition, pediatric human immunodeficiency virus wasting syndrome.***

ABBREVIATIONS. HIV, human immunodeficiency virus; LBM, lean body mass; IGF-1, insulin growth factor 1; BMI, body mass index; MAC, mid-arm circumference; TSF, triceps skinfold; AMA, arm muscle area; RNA, ribonucleic acid; REE, resting energy expenditure; RQ, respiratory quotient; CT, computed tomography; QOL, quality of life.

Nutritional issues relating to human immunodeficiency virus (HIV) -infected adults have received considerable attention without a corresponding focus in HIV-infected children. In adult studies, nutritional status and depletion of lean body mass (LBM) are predictive of survival, even after adjusting for age and CD4+ T-cell counts.[1,2] The relationship between depletion of LBM in children and survival has not been studied systematically, although decreases in LBM in children have been noted by Miller et al[3] and Dankner et al.[4] Failure to thrive affects 25% to 100% of children with symptomatic HIV infection and has been associated with shortened survival.[5,6] In addition, poor growth precedes decreasing CD4+ T-cell counts and the development of opportunistic infections.[6,7]

Malnourished HIV-infected adults have been treated with megestrol acetate, with weight gain and increased fat stores noted. However, Von Roenn et al[8] reported an increase in LBM, whereas Oster et al[9] did not. The study of Brady et al[10] of HIV-infected children demonstrated weight gain with megestrol acetate, but measurements of LBM were not performed. Furthermore, enteral or parenteral supplementation in children results in weight gain and increases in adipose stores but not in LBM.[11,12] The importance of LBM to survival and the difficulty in correcting loss of LBM in malnourished children with HIV underscore the need for therapies that enhance protein anabolism. Injectable anabolic steroids, medroxyprogesterone acetate, and stanozolol have increased muscle bulk, weight, strength, and a sense of well being in HIV-positive adults but have not been evaluated in children because of a high potential for adverse effects on growth and development.[13–15] Oxandrolone is a synthetic anabolic steroid

From the *Divisions of Clinical Immunology and Allergy, ‡Endocrinology, §Radiology, and ‖Gastroenterology, Children's Hospital Los Angeles, Los Angeles, California; ¶Vital Research, Los Angeles, California; and #Bio-Technology General Corporation, Iselin, New Jersey.

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Reprint requests to (S.F.) Division of Clinical Immunology and Allergy, Childrens AIDS Center, Mailstop 54, 4650 Sunset Blvd, Los Angeles, CA 90027. E-mail: sfox@chla.usc.edu

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having the chemical name 17β-hydroxy-17α-methyl-2oxa-5α-androstane-3-one. Structurally, oxandrolone is a derivative of testosterone but is unique among all other testosterone analogs in that it contains an oxygen atom instead of a methylene group at the 2 position of the phenantherene nucleus and lacks a 4-ene function in the A-ring. Oxandrolone has been approved by the Food and Drug Administration (NDA 13-718) in doses of up to 20 mg per day in adults for use as adjunctive therapy. It is indicated to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma. It also used for some patients, who, without definite pathophysiologic reasons, fail to gain or to maintain normal weight, to offset the protein catabolism associated with prolonged administration of corticosteroids and for relief of the bone pain frequently accompanying osteoporosis. Oxandrolone has been evaluated extensively for use in other pediatric conditions because of its safety profile and its oral availability.[16–20]

This open label pilot study was conducted to evaluate the safety and short-term effects of a 3-month course of oxandrolone given to malnourished HIV-infected children and to obtain preliminary information on the durability of any positive effects of the treatment after discontinuation of the study medication.

METHODS

Patient Selection

HIV-positive patients of ages 3 to prepubescent who had depleted LBM or were at risk for depletion were eligible to participate in this study. LBM depletion was defined as an arm muscle area (AMA) <5th percentile for age and gender, whereas risk for depletion was defined as an AMA between the 5th and 10th percentiles with a slowed weight growth velocity. Participants were required to be clinically stable, on antiretroviral therapy, managed as outpatients, have the written informed consent of a competent parent or guardian, and be willing and able to adhere to the protocol procedures and scheduled visits.

Subjects were excluded from participation if there were any clinically significant laboratory abnormalities, use of megestrol acetate 30 days before study, active opportunistic infection, or if they were receiving ketoconazole or ganciclovir.

Informed consent was obtained from the patient's parent/guardian(s) and assent was obtained from those patients >6 years of age. The institutional review board approved the protocol and written consent.

Treatment

In this unblinded prospective study, subjects received oxandrolone, .1 mg/kg by mouth once daily for 3 months. They were evaluated before beginning treatment, monthly for 3 months during treatment, and monthly for 3 months posttreatment. Each patient/parent/guardian received routine dietary counseling. Adjunctive exercise programs were not prescribed.

Clinical and Laboratory Monitoring

One to 4 weeks before beginning oxandrolone the following were performed, obtained, or calculated: physical examinations including Tanner staging, routine blood chemistries, complete blood counts, CD4+ T-cell numbers and percentages, HIV p24 antigen, quantitative HIV ribonucleic acid (RNA) polymerase chain reaction, T4, thyrotropin, insulin-like growth factor 1 (IGF-1), IGF base pair 3, triiodothyronine 3, reverse triiodothyronine 3, growth hormone, cortisol, insulin, prealbumin, and carotene. Nutritional assessments included weight, height, body mass index (BMI), skinfold measurements mid-arm circumference (MAC), triceps skinfold (TSF), arm muscle area (AMA) (calculated using the Heymsfield equation[19] [MAC (mm) ÷ 3.1416 − TSF (mm)]^2 × .785 = AMA mm^2), weight and height growth velocities, and resting energy expenditure (REE) with respiratory quotient (RQ).

Patients took oxandrolone once daily for 3 months. At study entry, after 3 months on oxandrolone and after 3 months off oxandrolone, patients had the above studies repeated. In addition, at these times computed tomography (CT) without contrast was performed at the first through third lumbar vertebra and on the left and right mid-humerus and left and right mid-femur. Cross-sectional areas of fat (cm^2) were obtained with the same scanner (General Electric Hilite Advantage, Milwaukee, WI) and the same mineral reference phantom for simultaneous calibration (CT-T bone densitometry package; General Electric Hilite Advantage). Bone age was measured radiographically on the left wrist. The techniques for these measurements have been described in detail previously.[21,22] REE including RQ using the Sensor Medics 2900 Metabolic Cart or Sensor Medics Vmax series 229 (Sensormedics, Yorba Linda, CA) were completed as well as quality of life (QOL) assessment questionnaires, developed by the Pediatric AIDS Clinical Trials Group.

All children had physical examinations, complete blood counts, blood chemistries, and evaluations for adverse effects monthly throughout the 6-month study. These subjects had been followed for ≥3 years by a registered dietitian who routinely recommended dietary manipulation, nutritional supplementation, or enteral feeds. These interventions were maintained throughout the study. Nutritional assessments including weight, height, BMI, weight and height growth velocities, MAC and TSF, appetite ratings, and 3-day diet histories were completed by the guardians and analyzed monthly using Nutritionist III-Diet Analysis (Hearst Corporation, San Bruno, CA). Weights were obtained using a Healthometer balance scale (Continental Scale Corporation, Chicago, IL). Heights were obtained using a Holtain-mounted stadiometer (Holtain Limited Crymych, Dyfed, UK). MAC was measured with an Inser-Tape (Ross Insertion Tape; Abbott Laboratories, Columbus, OH). Skinfold measurements were obtained using a Lange Skinfold Caliper (Cambridge Scientific Industries, Cambridge, MD). AMA was calculated using MAC and TSF.

Statistical Analysis

The data were entered into an American Standard Code for Information Interchange file and analyzed using the Statistical Package for the Social Sciences for Windows Version 6.1(SPSS Inc, Chicago, IL). For ease of interpretation, change scores were computed for some of the nutritional variables (weight, height, BMI, MAC, TSF, and AMA). All other variables were examined using raw values in this within-subjects statistical design.

The QOL questionnaire completed by the parents evaluated 5 areas: general health ratings, physical, psychological, social, and symptoms. Because the sample size was <20, the short-term and long-term effects of the treatment (efficacy) were examined using the Friedman two-way analysis of variance nonparametric test, which is appropriate for testing within subject differences over time in a 1-group design. The Friedman test uses the χ^2 statistic. Because of the exploratory nature of this study, α was set at .10 for the significance of the main effects. Because each variable for the efficacy component of the study was measured 3 or 4 times, post hoc analysis of variable pairs (preentry vs entry, entry vs end treatment, and end treatment vs end study) was conducted using the Friedman test, when the main effect was significant for family-wise error. α was set at .05 for significance of the post hoc tests.

RESULTS

A total of 10 patients (6 males 4–14 years of age and 4 females 7–12 years of age) enrolled in this study. None of the patients' values exceeded exclusionary values for clinical laboratory measures. One patient was diagnosed with cryptosporidium enteritis and disseminated *Mycobacterium avium* complex after 1 month on oxandrolone, and he was discontinued from the study. Therefore, 9 patients had evaluable data. Of the patients, 5 were Hispanic, 3 were black, and 1 was white. Of the patients, 8 were

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infected perinatally and 1 was transfusion-related. Of the patients, 4 were HIV classified as C3, 1 as C1, 1 as B3, 1 as B2 and 2 as A3. These patients had all been treated aggressively with antiretroviral therapy for at least 1 year before beginning Oxandrolone. Eight out of 9 patients were on triple antiretroviral therapy, including at least one protease inhibitor. One patient was on dual nucleoside reverse transcriptase inhibitors. All the patients had their drug cocktails changed once at various time frames during the study because of either an increasing HIV RNA polymerase chain reaction or an inability to tolerate the combination therapy.

Before entering the study, all subjects were losing weight with a declining BMI. During the prescriptive period, significant increases in weight (M = +1.2 kg; P = .002); BMI (M = +.51; P = .02); uninterrupted linear growth (M = +1.3 cm; P = .02); AMA as calculated from MAC and TSF (M = +25.8 cm^2; P = .02); and muscle by CT of the humerus (P = .05) and femur (P = .2) were observed (Fig 1). No changes by CT were seen in the vertebral area or in trabecular bone density. Weight, anthropometric, and body composition changes occurred despite an average calorie intake at 97% of recommended daily allowance by 3-day diet history. Average protein intake was 338% recommended daily allowance. Fat, as measured by TSF, was significantly decreased (M = −.75 mm; P = .05). Of the 9 patients, 6 had decreased fat stores by CT at the 3 sites scanned, but these did not reach statistical significance. A significant increase in femoral cortical bone area (P = .02) and cross-sectional area (P = .02) was found from baseline CT, compared with CT scans after taking oxan-

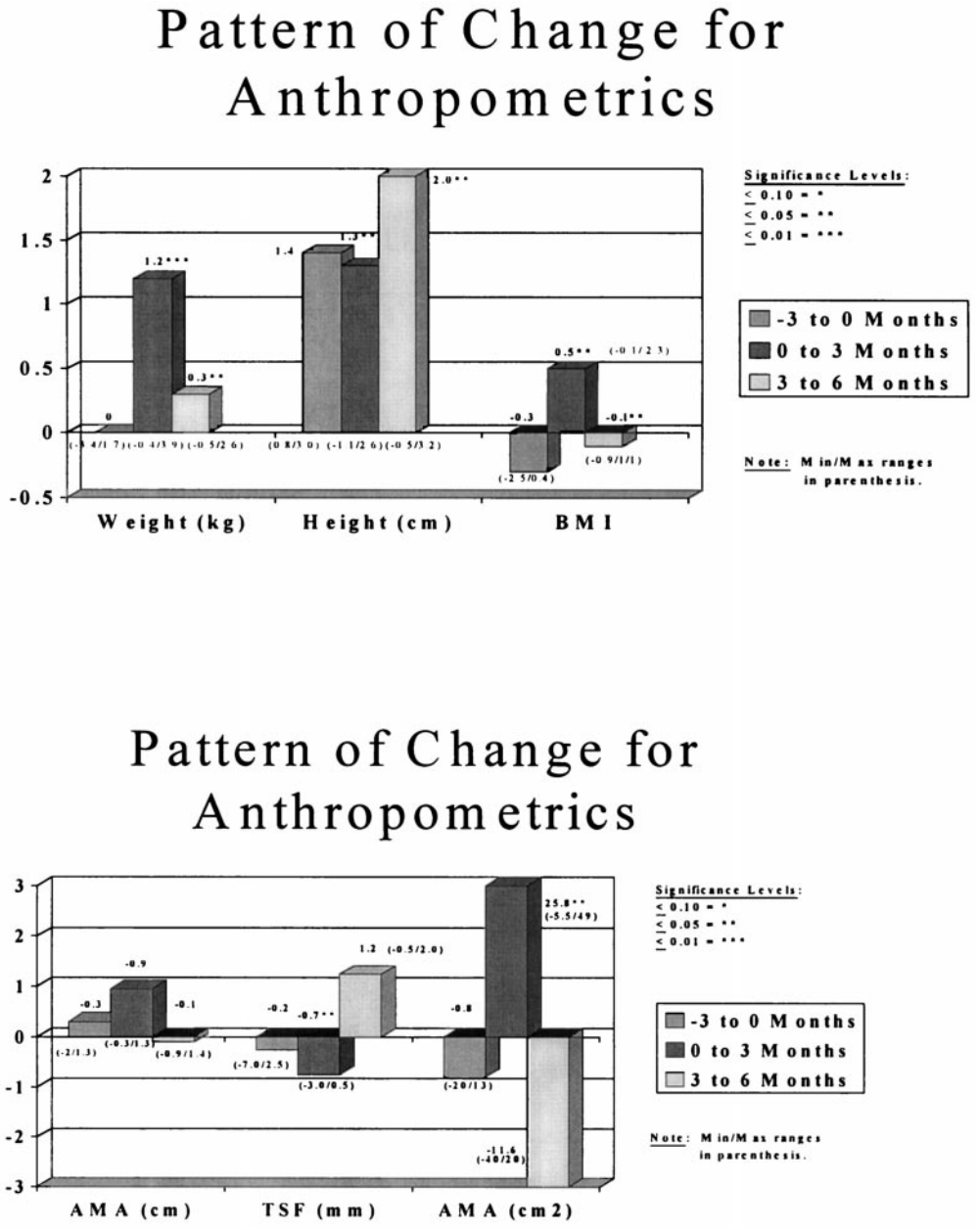

Fig 1. Median pattern of change of anthropometrics in 9 malnourished HIV-infected children 3 months before study entry, after 3 months of oxandrolone therapy, and 3 months after discontinuation of oxandrolone. Significance based on change from the previous 3 months.

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drolone for 3 months. Bone age did not change during the treatment period.

REE was elevated slightly in this sample at baseline: 106% of normal. RQ was within normal range with a $\bar{x}$ = .87. While receiving oxandrolone, there was no significant change seen in REE or RQ.

Significant laboratory findings during this period included an increase in IGF-1 (P = .004) and prealbumin (P = .002; Fig 2).

After 3 months off treatment, weight was maintained with an additional median gain of .3 kg. BMI decreased significantly (M = −.16; P = .02) but did not return to pretreatment levels, whereas linear growth increased significantly (M = +2.0 cm; P = .02). AMA, calculated from MAC and TSF and muscle mass by CT at the femur, humerus, and vertebra cross-sections, decreased from the treatment period but again did not reach pretreatment values, whereas fat, measured by TSF, increased significantly (M = +1.25 mm; P = .02). There continued to be no significant changes in fat composition noted in CT, although 5 of the 6 patients measured did have increases. Increased femoral cross-sectional area continued to increase significantly (P = .02), whereas femoral cortical bone area and trabecular bone density were maintained by CT. Bone age, REE, and RQ did not change. Laboratory findings after 3 months off oxandrolone resulted in a significant decrease in prealbumin (P = .008) while IGF-1 was maintained.

Because of the time and expense involved in CT

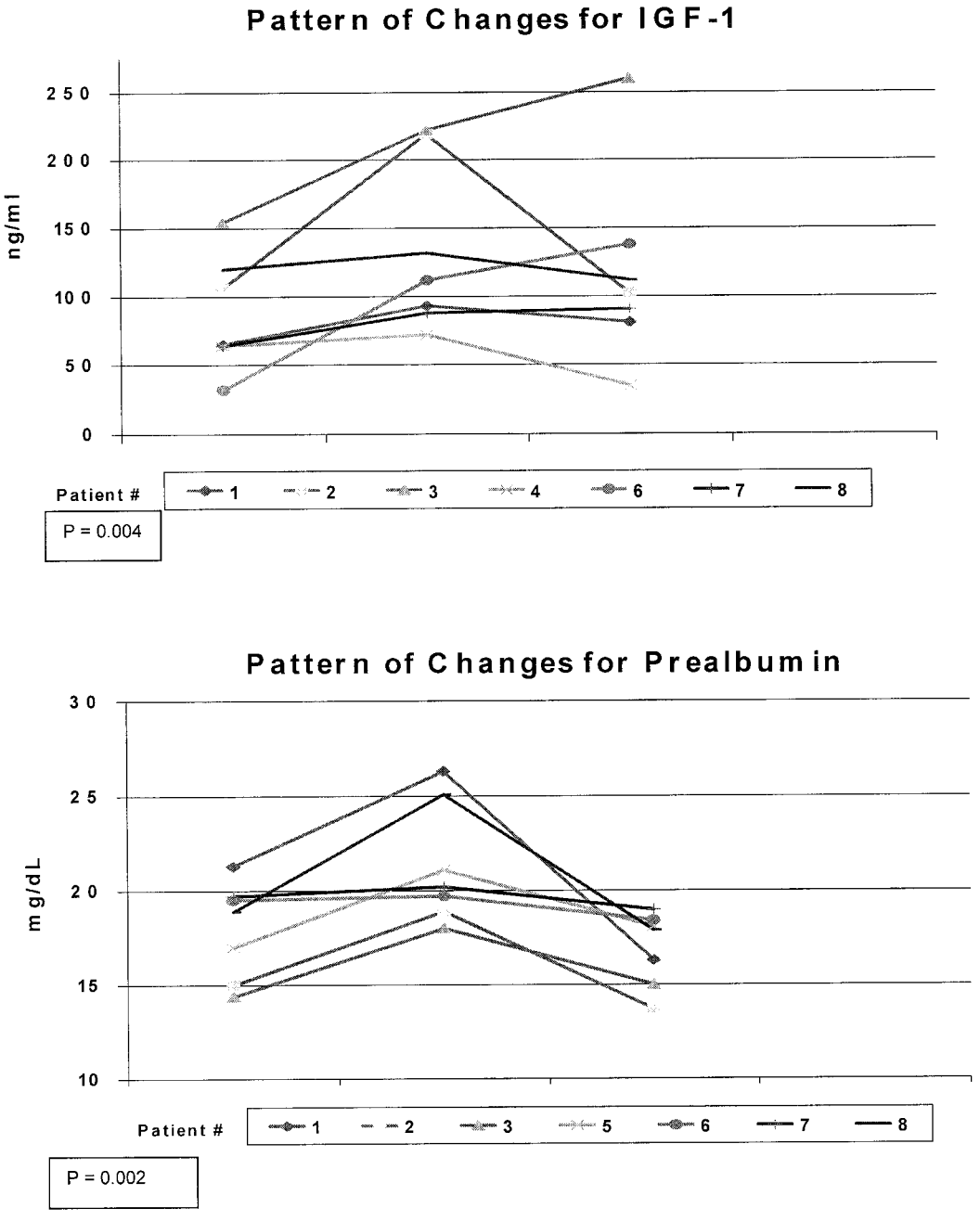

Fig 2. Pattern of changes of IGF-1 and prealbumin in 8 malnourished HIV-infected children at study entry, after 3 months on oxandrolone therapy, and 3 months after discontinuation of oxandrolone. Significance based on change from entry and end treatment.

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scanning, it was of interest to examine the validity coefficients between the anthropometric tests and the CT findings of fat and muscle in the arm, trunk (reflecting abdominal fat), and leg. Spearman correlations were high for corresponding measurements (preentry, end of treatment, and end of follow-up) for all anatomic areas scanned (rho = .61–1.0) and were completely redundant in the arm, anatomically most associated with the triceps muscle (rho = 1.0, .99, and .99) across the 3 time periods with data available from 7 subjects (Fig 3A).

Likewise, validity coefficients between the AMA calculations and the CT findings of muscle in the trunk, leg, and arm were examined. Spearman correlations were high for corresponding measures for all anatomic areas scanned (rho = .69–.97). The 2 measures were almost completely redundant in the leg (rho = .97) across the 3 time periods with data available from 7 subjects. Redundancy was nearly as strong in the arm (rho = .93, .93, and .72) across the 3 time periods with data available from 7 subjects (Fig 3B).

The high degree of stability of the energy expenditure variables (percentage and RQ) was of interest. These measures showed high to acceptable internal consistency reliability (coefficient α = .96 and .74, respectively) over 4 measurements. The findings suggest that energy expenditure can be measured reliably for individual clinical decision-making.

There were no clinically relevant changes in chemistry, hematology, or other endocrine studies. CD4 + T-cell counts were M = 167 cells/μL (range: 13–1377) at entry, M = 123 (range: 9–1371) at end treatment, and M = 167 (range: 19–1481) at follow-up. CD4+ T-cell percentages were M = 15% (range: 1%–36%) at entry, M = 17% (range: 1%–38%) at end treatment, and M = 18% (range: 2%–40%) at follow-up. HIV p24 antigen and HIV RNA did not change significantly throughout the duration of the study. Median HIV RNA was M = 4.7 Log 10 (range: 3.64–5.39) at entry, M = 4.5 Log 10 (range: 3.87–5.46) at end treatment, and M = 4.34 Log 10 (range: 1.5–5.45) at follow-up. No changes in Tanner staging or virilization were observed.

No significant changes were seen in any of the areas evaluated in the QOL questionnaire, although a possible trend was seen in the social subscale with a decline noted from pretreatment to the end of the study (P = .058).

DISCUSSION

The effective management of malnutrition in HIV-infected children requires an intervention that improves LBM. In HIV-infected adults, LBM increased after treatment with virulizing testosterone-based anabolic steroids, but this approach is inappropriate in children. Oxandrolone, an anabolic steroid with minimal if any virulizing effects, has been used safely in children for 21 years for a variety of indications.[17–21] The results of the present study suggest that a 3-month course of oxandrolone was easily administered, well-tolerated, and safe in 9 HIV-infected, malnourished children. The results also indicate that oxandrolone treatment improves nutritional status, evidenced by an accelerated rate of weight gain, increased BMI, increased muscle mass, and decreased fat stores by skinfold, compared with pretreatment values. The improvement of serum prealbumin levels observed during treatment supports the anthropometric results. These measurements of nutritional status occurred without a prescribed exercise program and without a significant change in calorie or protein intake. Increase in height growth was statistically significant throughout the study; however, it was not considered to be clinically significant because it did not vary from pretreatment changes and reflected normal growth velocity in a pediatric population.

There were excellent correlations between results obtained by CT and skinfold calculations for measurements of muscle and fat changes with treatment (correlation coefficients = .9 and 1.0, respectively). There were significant changes seen in fat by TSF. Although the majority of patients had similar correlations by CT suggesting a trend, the changes did not reach significance. This may be attributed to the fact that fewer subjects received CT than TSF evaluations because of the addition of CT of the humerus to the protocol after the second subject. These findings suggest that TSF and AMA measurements conducted by the same skilled clinician over time can provide accurate fat and muscle assessments for individual clinical decision making.

A small weight increase and muscle decrease were observed after active therapy was discontinued, but changes did not reach statistical significance. Of interest is the fact that although Fig 1 demonstrates a decrease in the AMA seen in the 3- to 6-month follow-up period, the decline was less than half of the increase seen during the 3-month treatment period. However, if the trends observed continued, as seems likely, body composition measurements would return to baseline. Serum albumin remained unchanged throughout the 6-month course of the study. In contrast, serum prealbumin sharply increased during treatment and rapidly declined during the 3-month follow-up period, despite consistent dietary intake. This further supports the assertion that utilization of nutrients is improved in patients receiving oxandrolone. IGF-1 measures growth hormone adequacy, effects of sex steroids, and nutritional status. This laboratory value increases with age (especially during puberty) and with improved nutrition and health. The increases seen during the treatment period and 3-month follow-up could further support the role of oxandrolone in improving malnutrition. Increase in IGF-1 in all older children in this study does not seem to be attributable to the entrance of puberty, because there were no increases in Tanner staging, a finding similar in the younger cohort. However, because basal and poststimulation with leutinizing hormone-releasing hormone, sex steroids, or gonadatropins were not measured, we cannot ensure that there was not some initiation of puberty as a result of the treatment. Some clinicians are concerned about using anabolic therapy because of the potential for premature epiphyseal fusion. Multiple studies of the use of oxandrolone in girls

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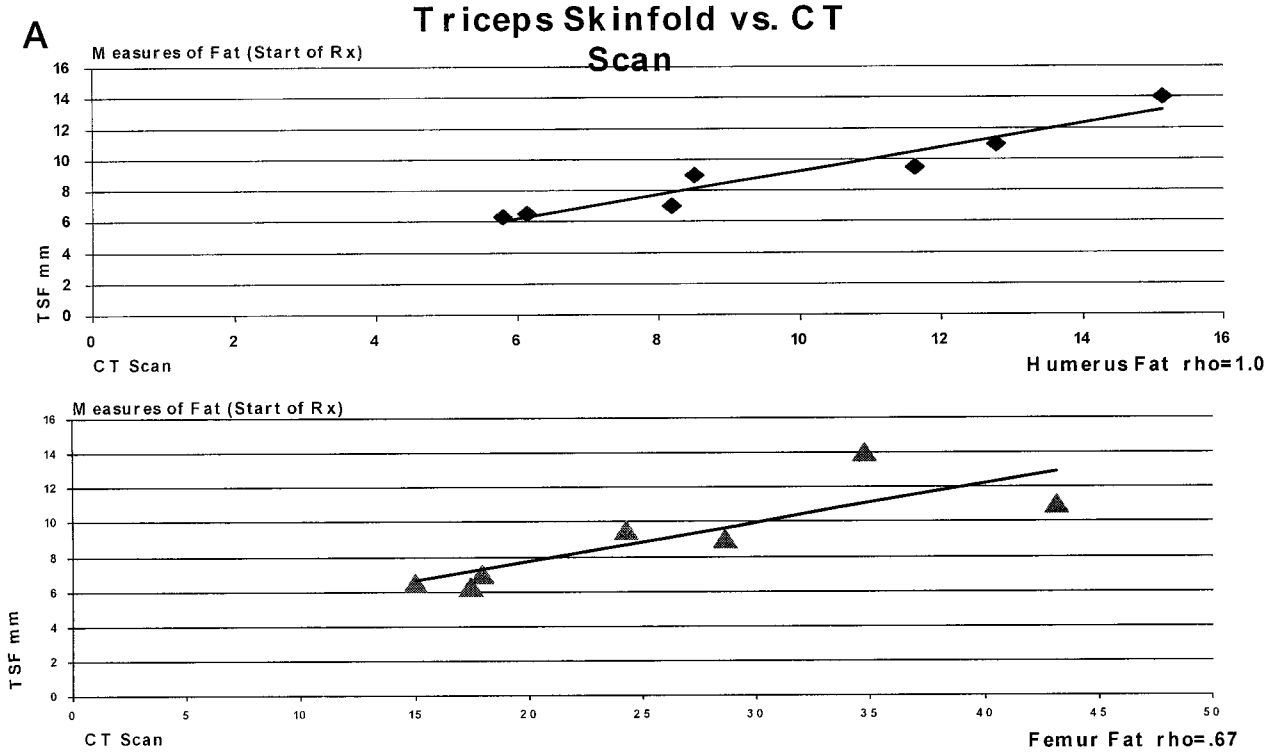

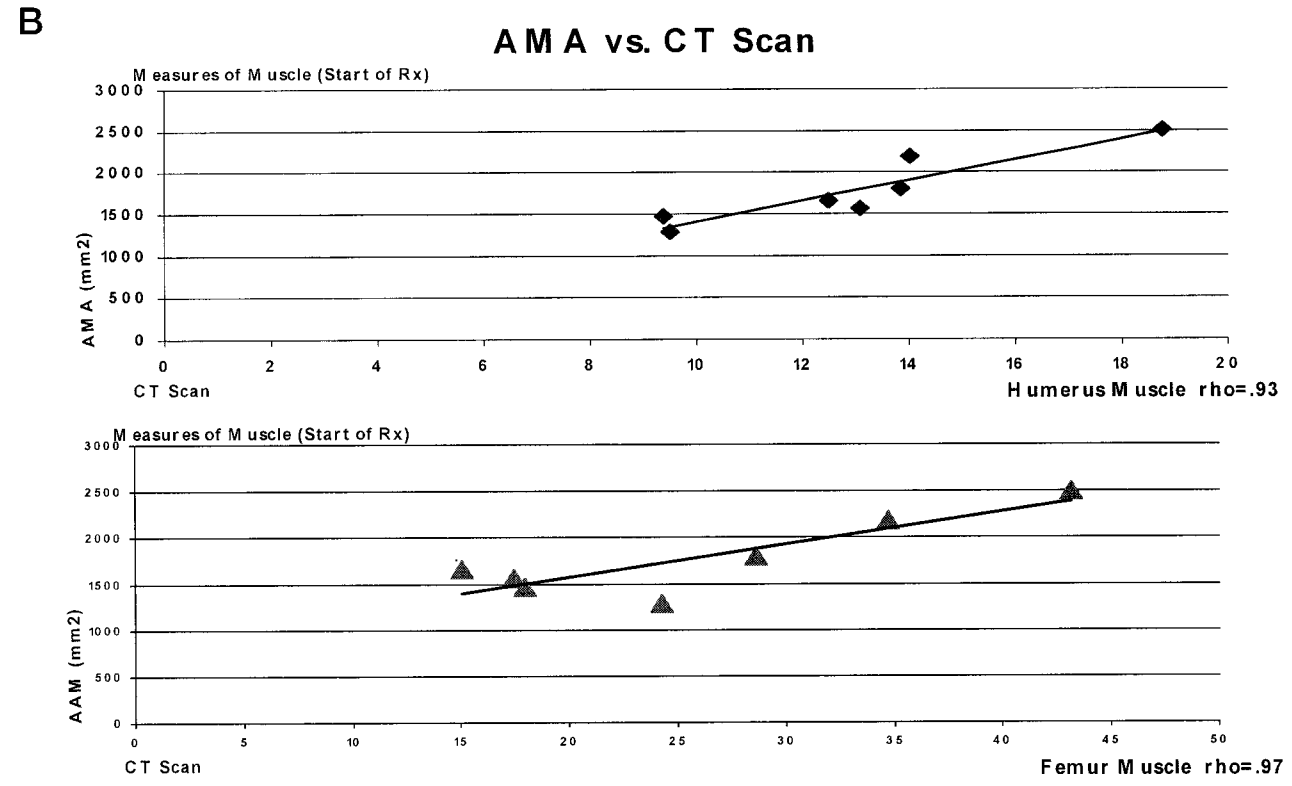

Fig 3. A, Comparison of the measurement of fat by TSF measurements versus CT of the humerus and femur at study entry in 7 malnourished HIV-infected children. B, Comparison of the measurement of muscle by AMA measurements versus CT of the humerus and femur at study entry in 7 malnourished HIV-infected children.

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with Turner syndrome[18] and boys with constitutional delay in growth and puberty[24] indicate that oxandrolone can be used safely and effectively without altering final height. Anabolism and improved nutritional status in the presence of a stable metabolism as measured by REE and RQ as well as macronutrient intake further supports an assumed improved utilization of nutrients with the use of oxandrolone.

The social subscale was the only area in the QOL questionnaire that suggested a significant change during the study. This area within the questionnaire focuses primarily on school issues and attendance. Participation in the study required extra time away from school and also the majority of these patients are C classified, suggesting these patients have more symptoms and advanced disease, which may explain the decline in this score. The lack of significant changes in the other areas of general health ratings, physical functioning, psychological well-being, or symptoms is of interest, although, anecdotally, 4 of the 9 children chose to resume oxandrolone at the end of the study.

Of the 10 patients initially enrolled in this trial, 2 failed to respond to the intervention. The first child, an 8-year-old girl, consumed only ~80% of the estimated caloric needs during the treatment. This was likely associated with psychosocial and environmental conditions, which interfered with dietary intake. After completion of the treatment phase of the trial, this child's foster care placement was changed and this was associated with improved caloric intake and growth. Although a prescribed exercise regimen was not necessary for a positive effect of oxandrolone in the patients in this trial, adequate caloric intake is essential for anabolic therapy to be effective.

The second child, a 9-year-old boy, was wasting actively at the time of study entry and was considered a treatment failure, despite adequate caloric intake provided through gastrostomy tube feedings. Within 4 weeks of beginning oxandrolone, cryptosporidium and *Mycobacterium avium* complex were diagnosed and were associated with severe malabsorption. This again emphasizes the need to provide adequate calories without excessive losses to realize the benefit of anabolic intervention.

Several limitations affect interpretation of our findings: sample size is small in this pilot study, no control group was included, and multiple statistical tests were conducted on the data possibly inflating α beyond that which was controlled for. However, oxandrolone was remarkably well-tolerated; no adverse effects were observed and objective measures of growth and protein anabolism were consistent with positive effects of this intervention in malnourished, HIV-infected children. Future studies should assess the potential additional benefits or risks of a longer or higher dose therapy or similar cyclical dosing schedule with school-aged versus prepubescent cohorts.

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Evaluation of the Effects of Oxandrolone on Malnourished HIV-Positive Pediatric Patients

Sarah Fox-Wheeler, Linda Heller, Cathleen M. Salata, Francine Kaufman, M. Louisa Loro, Vincente Gilsanz, Michael Haight, Gwenn C. Umman, Norman Barton and Joseph A. Church

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