Alendronate, Vitamin D, and Calcium for the Treatment of Osteopenia/Osteoporosis Associated With HIV Infection

Kristin Mondy, MD, William G. Powderly, MD,* Sherry A. Claxton, RD,* Kevin H. Yarasheski, PhD,† Michael Royal, RPh,* John S. Stoneman, RN,* Mary E. Hoffmann, RN,* and Pablo Tebas, MD‡*

Background: Osteopenia and osteoporosis are frequent complications of HIV infection and/or its treatment. Alendronate is the only bisphosphonate approved for the treatment of osteoporosis in men and women. We conducted a 48-week prospective, randomized, open-label study to evaluate the effects of alendronate, vitamin D, and calcium supplementation on bone mineral density (BMD) in patients with HIV infection.

Methods: Thirty-one HIV-infected subjects with lumbar spine BMD *t*-scores less than −1.0 on antiretroviral therapy for a minimum of 6 months were randomized to receive (n = 15) or not to receive (n = 16) 70 mg of alendronate weekly for 48 weeks. All subjects received calcium (1000 mg daily as calcium carbonate) and vitamin D supplementation (400 IU daily). The study was powered to detect 3% changes in BMD in the lumbar spine within arms at 48 weeks.

Results: Thirty-one patients were enrolled; most were male, with an average length of HIV infection of 8 years. Eighty-four percent had an HIV RNA load below 400 copies/mL, with a current median $CD4^+$ T-cell count of 561 cells/mm^3 (median nadir CD4 cell count of 167 cells/mm^3). At baseline, the median *t*-score in the lumbar spine was −1.52 and the median *t*-score in the hip was −1.02. Alendronate in combination with vitamin D and calcium increased lumbar spine BMD by 5.2% (95% confidence interval [CI]: 1.3–6.4) at 48 weeks compared with an increase of 1.3% (95% CI: −2.4 to 4.0) in subjects receiving vitamin D and calcium alone. One subject discontinued treatment in each arm. There were no serious adverse events.

Conclusions: Alendronate, vitamin D, and calcium are safe and potentially useful in the treatment of osteopenia/osteoporosis associated with HIV infection.

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From the *Washington University School of Medicine, Division of Infectious Diseases, St. Louis, MO; †Washington University School of Medicine, Division of Endocrinology, St. Louis, MO; and ‡University of Pennsylvania, School of Medicine, Division of Infectious Diseases, Philadelphia, PA.

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Reprints: Pablos Tebas, University of Pennsylvania, Division of Infectious Diseases, 502 Johnson Pavilion, 3610 Hamilton Walk, Philadelphia, PA 19104-6073 (e-mail: Pablo.Tebas@uphs.upenn.edu).

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Recently, several groups have reported an increased incidence of osteopenia/osteoporosis among patients living with HIV.[1–4] Other bone complications, such as avascular necrosis of the hip, have also been reported.[5] Initially, a specific drug class, protease inhibitors (PIs), was blamed for what was considered then to be a new side effect of therapy.[1,6] Soon, it became clear that osteopenia and osteoporosis are also frequent in the absence of therapy.[7–9] In a large recent trial, the prevalence of osteopenia among antiretroviral-naive HIV-positive individuals was approximately 28%, 1.5 times what would be expected for the general population.[10] Case series that have included patients with more advanced HIV disease who have received treatment for longer periods have reported prevalences of 40% to 50%,[1,11,12] making this complication one of the most frequent metabolic problems associated with HIV disease. The relative contribution of antiretroviral treatment and HIV infection itself to the development of this problem and its relation to other metabolic complications like lactic acidosis, lipodystrophy, and hyperlipidemia are still under study.[3] In addition, HIV-infected individuals may have numerous risks for secondary causes of osteoporosis, including low weight or prior wasting, a history of steroid use, poor nutrition, hypogonadism, a history of prolonged immobilization, or other chronic illnesses.[12] Any single factor or combination of these factors may be important contributors to the premature and ongoing loss of bone mineral density (BMD) in this patient population.

Despite the limited knowledge of the causal factors involved in the development of osteopenia in HIV-infected individuals, the reported prevalence of low BMD in patients with HIV infection has remained high. Furthermore, as more people live longer with HIV and continue to take antiretroviral medications for extended periods, it has become even more important to find adequate therapies to counteract the long-term complications likely associated with highly active antiretroviral therapy (HAART) and/or HIV infection itself.

Currently, alendronate, a bisphosphonate, is approved in the United States for the treatment of osteoporosis in men and women. Although there are anecdotal reports of its use in patients with HIV infection,[13] it has not been evaluated

systematically. It is an attractive candidate for use, given its few side effects, few drug interactions, and convenient once-weekly dosing. Therefore, we designed a prospective, randomized, open-label pilot trial of alendronate in HIV-infected individuals with osteopenia or osteoporosis on HAART to see if alendronate treatment could stabilize and prevent further BMD loss in these patients.

PATIENTS AND METHODS

Design

We conducted a prospective, randomized, open-label trial of alendronate over a 48-week period in 31 HIV-infected individuals on HAART with osteopenia or osteoporosis (defined according to World Health Organization criteria) to see if alendronate treatment could stabilize and prevent further BMD loss. The primary end point of the trial was a change in BMD in the lumbar spine. The study was powered to detect 3% differences within arms. During the study period, patients were followed for changes in BMD, safety and tolerability of alendronate, and changes in serum and urine bone markers. The study was approved by the Human Studies Committee of the Washington University Medical Center.

Patient Population

HIV-infected individuals with evidence of osteopenia/osteoporosis (ie, with lumbar spine BMD *t*-scores less than −1.0) on HAART for a minimum of 6 months were recruited from the Washington University AIDS Clinical Trials Unit (ACTU) and the Infectious Diseases outpatient practice at Washington University School of Medicine. The HAART regimen had to include at least 1 PI or nonnucleoside reverse transcriptase inhibitor (NNRTI) for the 6 months before enrollment and for the duration of the study thereafter. Individuals with peptic ulcer disease; esophagitis; known intolerance to alendronate or other bisphosphonates; current abnormalities of estrogen, testosterone, parathyroid, or thyroid hormone (all determined at baseline); concurrent use of drugs with known effects on bone metabolism (ie, heparin, foscarnet, anticonvulsants, growth hormone); or other metabolic bone diseases were excluded from the study. Patients with recent prolonged bedrest, alcohol abuse, a concurrent opportunistic infection, malignancy, or a life expectancy of less than 1 year were also excluded. Patients with hypogonadism on stable replacement therapy were allowed in the study.

Treatment Regimen

Patients were randomized to receive 70 mg of alendronate weekly or no study drug for 48 weeks. All subjects received calcium supplements (1000 mg daily as calcium carbonate) and vitamin D supplements (400 IU daily) for the duration of the study, because this was considered minimal standard-of-care treatment for individuals with low BMD. Randomization of patients and follow-up drug counts were coordinated by the ACTU pharmacist, with subjects receiving the study drug and vitamin supplements in bottles for self-administration.

Enrollment and Monitoring

At baseline, all subjects underwent a clinical evaluation, dual-energy x-ray absorptiometry (DEXA) scan, and complete medical and social history evaluation to determine eligibility. Patients who were subsequently enrolled received additional clinical evaluations every 4 weeks for the first 8 weeks and then every 12 weeks thereafter to monitor for any adverse events. All subjects had a DEXA scan at baseline and at 24-week intervals to assess whole-body BMD, adipose and lean tissue regional distributions, lumbar spine BMD, and proximal hip BMD.

Bone metabolism parameters (ie, bone-specific alkaline phosphatase, osteocalcin) were obtained after an overnight fast before the administration of the study drug (baseline) and at 12-week intervals. Urine studies of bone metabolism (24-hour creatinine, calcium, pyridinolines, and deoxypyridinolines) were obtained at baseline and at 24-week intervals. Safety laboratory parameters, including a complete blood cell count, serum electrolytes, and liver function tests, were obtained at study enrollment and at 12-week intervals. CD4 cell counts and HIV RNA levels were also obtained at 12-week intervals as part of standard clinical care.

Bone Mineral Density Measurements

A Hologic QDR-2000 enhanced-array whole-body DEXA scanner and software (v5.71A) (Hologic, Waltham, MA) were used to measure bone mass. Regional array software (v4.74A:1) was used to determine BMD of the whole body, lumbar spine (L1–L4), and proximal femur. Each scan was acquired and processed by a Hologic-certified radiology technologist.

Laboratory Measurements

Serum bone alkaline phosphatase was measured with the chemical inhibition and differential inactivation assay (Mayo Medical Laboratories, Rochester, MN), with normal reference intervals of 24 to 146 U/L. Serum intact osteocalcin (OC) was measured by radioimmunoassay (Mayo Medical Laboratories), with normal reference intervals of 8 to 52 ng/mL. Urine pyridinolines and deoxypyridinolines were measured with the pyridinoline-deoxypyridinoline U high-pressure liquid chromatography (HPLC) assay (Mayo Medical Laboratories), with normal reference intervals of 18 to 40 nmol/mmol creatinine for men and 20 to 62 nmol/mmol for women (pyridinolines) and 5 to 14 nmol/mmol for men and 5 to 22 nmol/mmol for women (deoxypyridinolines). Because of the diurnal variation of crosslink excretion, only first morning urine samples were used. All other laboratory tests were performed by a central laboratory (Barnes-Jewish Hospital, St. Louis, MO).

Statistical Analysis

The primary end point of the trial was change in BMD in the lumbar spine region. The study was powered to detect a 3% within-arm difference in BMD in the lumbar spine by week 48 of the trial. Multiple repeated-measures ANOVA was used to evaluate changes in BMD between the 2 arms. If significant differences were found, multiple comparisons with baseline

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were performed applying the Bonferroni correction. SPSS 11.5 was used in all calculations.

RESULTS

Thirty-one subjects participated in the trial. Sixteen were randomized to receive vitamin D and calcium; in addition, 15 received 70 mg of alendronate weekly. Most patients were male (87%) and white (80%). The mean patient age was 44 years. Subjects had been infected with HIV for an average of 8 years. Sixty-one percent were receiving PI-based antiretroviral therapy (10 patients were taking indinavir, 2 were taking nelfinavir, 2 were taking lopinavir/ritonavir, and 5 were taking other PIs). One patient substituted stavudine for abacavir after 24 weeks of treatment. Most of them had undetectable HIV RNA viral loads at the time of enrollment. The current median CD4 cell count was 561 cells/μL, and the nadir CD4 cell count was 167 cells/μL. The mean body mass index was 25 kg/m^2. Twenty-nine percent of the patients were current smokers, and 16% were moderate drinkers. Baseline characteristics were well balanced between the 2 groups (Table 1). Patients with hypogonadism or hyper- or hypothyroidism were not eligible for the study. Two male participants were on stable androgen replacement therapy.

After 48 weeks, the change in BMD from baseline was measured. The effect of time in changes of BMD was analyzed using repeated-measures ANOVA, with time of measurement (baseline, week 24, and week 48) as a within-subjects factor. The sphericity assumption was met. The main effect of time of measurement was significant (F = 16.29, $P < 0.0001$). There was a significant difference between the alendronate group and the vitamin D and calcium group (F = 12.6, $P = 0.002$). Posthoc comparisons performed using the Bonferroni adjustment for multiple comparisons revealed that the main change in BMD in the lumbar spine at 48 weeks (95% CI) in the alendronate group was 5.2% (1.3–6.4) versus 1.3% (−2.4 to 4.0) in the vitamin D and calcium group ($P = 0.007$). The difference was also significant by week 24 (4.4% vs. 1.2%; $P = 0.02$; Fig. 1).

The changes in BMD were less marked in other anatomic regions, with no significant differences between arms (Fig. 2). The increases in BMD did not correlate with baseline *t*-scores, suggesting that the beneficial effects of alendronate were similar among different degrees of osteopenia/osteoporosis at baseline.

There were reciprocal changes in markers of bone formation, with significant decreases in bone alkaline phosphatase and osteocalcin as well as in markers of bone resorption (urine pyridinolines and urine deoxypyridinolines) (Fig. 3). These were the expected changes if alendronate was working as an inhibitor of bone resumption.

Two patients discontinued the study (1 in each arm before completing the study) for reasons unrelated to toxicity. Their baseline information was included, but they were not included in the effectiveness analysis. There were no serious adverse events related to the use of alendronate, which was well tolerated by participants. There were no changes in the background antiretroviral regimens.

TABLE 1. Baseline Characteristics

Characteristic*	Alendronate† (n = 15)	Vitamin D + Calcium† (n = 16)	Whole Group (n = 31)
Age (y)	46 ± 2	43 ± 2	44 ± 1.5
Gender (male/%)	14/93%	13/81%	27/87%
Race (white/%)	12/80%	13/81%	25/81%
Median nadir CD4 count (cells/μL)	186 ± 37	151 ± 29	162
Years HIV$^+$	8.3 ± 1.2	7.7 ± 1.3	8 ± 1.2
HAART regimen (PI/NNRTI)			
Nonsmoker/smoker	10/5	12/4	22/9
Alcohol use (yes/no)	7/8	4/12	11/20
Weight (kg)	77 ± 3	70 ± 3	74 ± 2
Body mass index	25.3 ± 0.9	24.6 ± 0.7	25 ± 0.6
Spine BMD	0.92 ± 0.02	0.91 ± 0.02	0.91 ± 0.01
Hip BMD	0.84 ± 0.03	0.89 ± 0.04	0.87 ± 0.02
Lumbar *t*-score	−1.70 ± 0.17	−1.60 ± 0.27	−1.64 ± 0.16
Hip *t*-score	−1.33 ± 0.15	−1.01 ± 0.23	−1.16 ± 0.14
% osteoporosis lumbar spine (no./%)	2/14%	4/25%	6/19%
Bone alkaline phosphatase (U/L)	158 ± 18	170 ± 18	164 ± 12
Osteocalcin	15.3 ± 1.1	20.9 ± 3.0	18.2 ± 1.7
Urine pyridinoline (nmol/mmol of creatinine)	41.1 ± 3.6	39.8 ± 2.1	40.4 ± 2
Urine deoxypyridinoline (nmol/mmol of creatinine)	9.2 ± 1.3	7.7 ± 0.6	8.4 ± 0.7
24-hour urine calcium (mg/24 h)	188 ± 44	209 ± 35	199 ± 28

*Mean ± SEM unless stated.
†There were no significant differences between the 2 groups.

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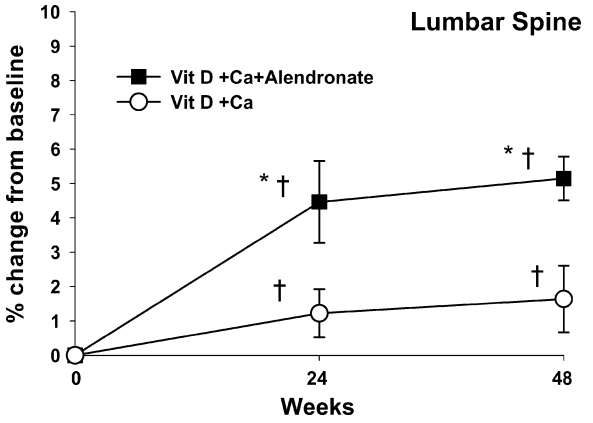

FIGURE 1. Changes in bone mineral density (±SEM) in the lumbar spine (primary end point of the trial) after 48 weeks of alendronate, vitamin D (Vit D), and calcium (Ca) versus vitamin D and calcium alone. *Significant change from baseline ($P < 0.05$). †Significant difference between arms ($P < 0.05$).

DISCUSSION

In the present study, once-weekly alendronate effectively increased BMD in HIV-infected subjects with osteopenia/osteoporosis. Although the BMD increases were greatest in the lumbar spine, moderate increases that did not reach statistical significance were also seen in the hip and total body and were evident within 6 months after beginning alendronate therapy and sustained throughout the duration of the study. Additionally, all subjects tolerated the drug well, and there did not seem to be any interactions with the concurrent use of multiple HIV-related medications, including nucleoside reverse transcriptase inhibitors (NRTIs), PIs, and NNRTIs.

In the past, alendronate has proven to be effective in improving BMD in men and women with primary or known secondary causes of osteoporosis.[14–16] Although the underlying mechanisms responsible for accelerated BMD loss in HIV-infected individuals remain unknown, an important goal of this study was to determine if alendronate could be effective in HIV-infected men and women currently on a variety of HAART regimens, especially because the use of such medications (especially PIs and NRTIs) has been postulated as an important contributor to the development of osteopenia.[1] Before this study, there were only anecdotal reports of the success of alendronate in HIV-infected individuals on HAART.[13] In our prospective study, even though the number of patients was small, we found alendronate to be effective regardless of the type of HAART regimen, duration of therapy, or duration of HIV infection. The changes were seen mainly in the lumbar spine and not in other regions. This was not unexpected, because early alendronate effects are more marked in the lumbar spine, which was the primary end point site in registration trials. To see an effect in other regions, a larger or longer study is necessary.

Interestingly, we found that many of the subjects randomized to take only calcium and vitamin D had a moderate but not statistically significant increase in BMD by the end of the study, suggesting that other more common factors associated with low BMD (ie, inadequate nutritional intake) may be important in the development of osteopenia in the HIV-infected population. We recently performed a cross-sectional study of 125 HIV-infected individuals with low BMD and found that a substantial proportion (70%) had calcium intake below the recommended daily allowance in the United States and that many individuals had multiple other risk factors for osteopenia, including smoking, low weight or history of

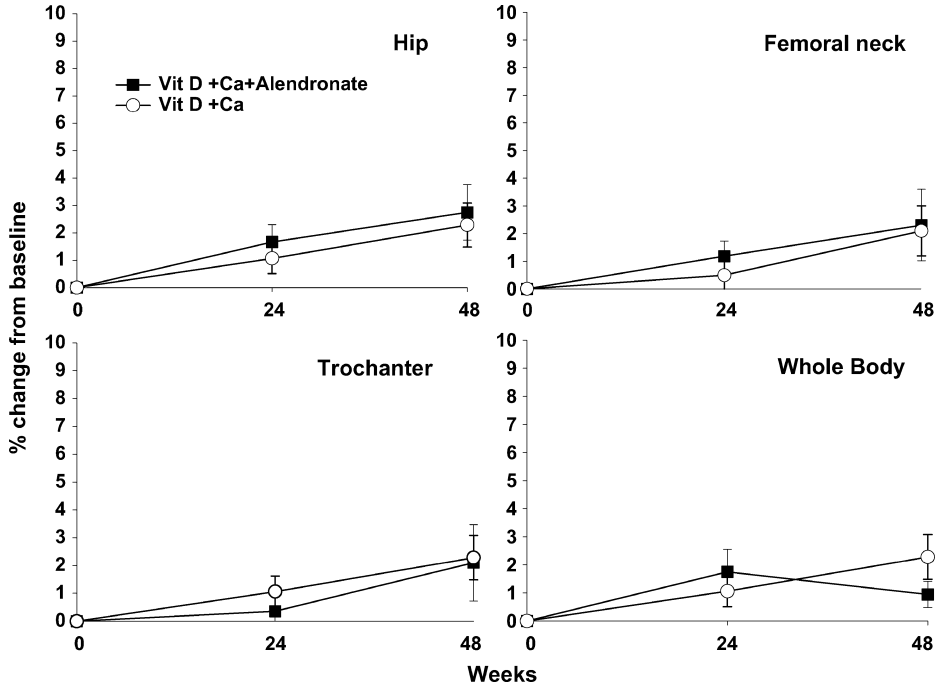

FIGURE 2. Changes in mean bone mineral density (±SEM) in other anatomic regions. No significant differences from baseline or between arms were observed. Ca indicates calcium; Vit D, vitamin D.

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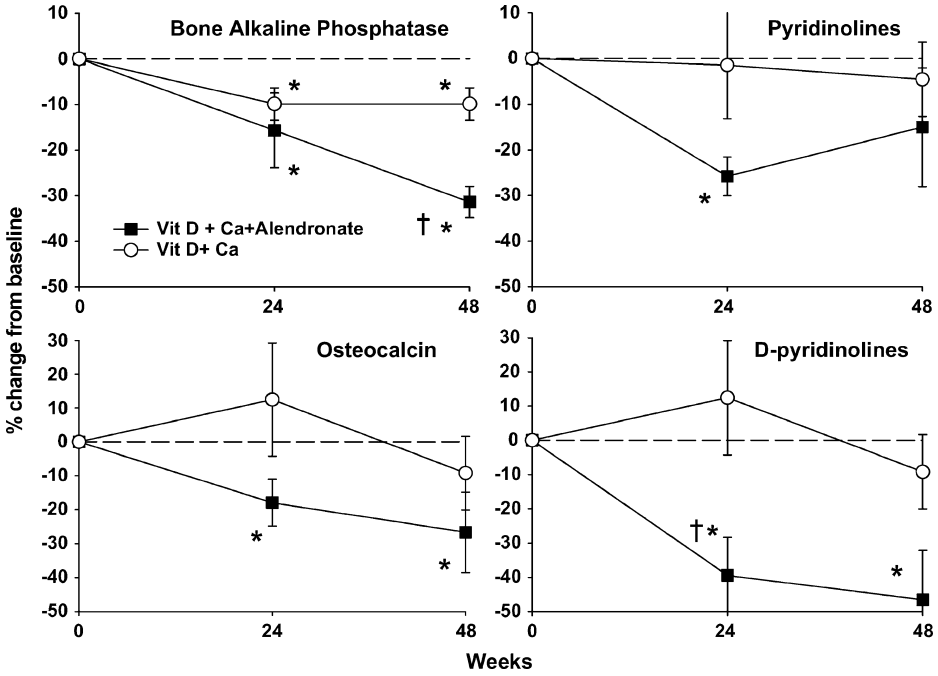

FIGURE 3. Changes (±SEM) in markers of bone formation and resorption. *Significant change from baseline ($P < 0.05$). †Significant difference between arms ($P < 0.05$). Ca indicates calcium; Vit D, vitamin D.

wasting, and a history of steroid use.[12] It thus seems strongly advisable for any physician involved in the care of an HIV-infected patient with proven osteopenia/osteoporosis to assess nutritional factors and potentially reversible causes of ongoing osteopenia carefully when considering additional drug therapies. All patients considered for a trial of alendronate therapy should also be strongly encouraged to take calcium and vitamin D supplements and engage in a moderate level of exercise if possible.

Given the high prevalence of osteopenia reported among HIV-infected individuals, it seems reasonable to assess individual risk for low BMD periodically throughout the course of HIV infection by obtaining a detailed history, physical, and nutritional evaluation. Patients who are thought to be at substantial risk for osteopenia should subsequently undergo DEXA scanning for definitive diagnosis.[17] Until the pathogenesis of osteopenia in HIV-infected patients is determined, it may be reasonable to try potential therapies other than alendronate, such as hormone replacement (if a patient has evidence of hypogonadism) or calcitonin (especially if a patient has established fractures or chronic bone pain). Unfortunately, none of these alternative therapies have been studied prospectively in HIV-infected patients.

Our study should not be interpreted as a recommendation for treatment of all HIV-positive patients with osteopenia. We think that treatment recommendations for HIV-infected patients, in the absence of large trials, should be consistent with standard national and international guidelines. Current guidelines for the treatment of osteoporosis in women recommend treatment of individuals with 1 major or 2 minor risk factors for osteoporosis plus a *t*-score lower than −1.5 on a DEXA scan.[18]

Given the results of our study, we think that alendronate is a safe, convenient, and effective option for treatment of osteopenia or osteoporosis in HIV-infected individuals on HAART who otherwise require it. Our study has limitations, however. First, it is based on changes of BMD, an accepted surrogate marker for a decreased risk of fracture, which is the outcome to prevent in the population. Second, although the study has a positive result is relatively small in size and included only a limited number of women, larger studies, including a more diverse patient population, are needed to confirm our findings.

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