

Zoledronic Acid Versus Alendronate for the Prevention of Bone Loss after Heart or Liver Transplantation

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Context: The first year after transplantation is characterized by rapid bone loss.

Objective: The aim of this study was to compare zoledronic acid (zoledronate) and alendronate for prevention of transplantation bone loss.

Design and Setting: A randomized clinical trial was conducted at a transplantation center.

Patients: The study included 84 adults undergoing heart or liver transplantation and a concurrently transplanted, nonrandomized reference group of 27 adults with T scores greater than -1.5 .

Interventions: Alendronate (70 mg weekly for 12 months) or one 5-mg infusion of zoledronate were both initiated 26 ± 8 d after transplantation.

Main Outcome Measures: The primary outcome was total hip bone mineral density (BMD) 1 yr after transplantation. Secondary outcomes included femoral neck and lumbar spine BMD and serum C-telopeptide, a bone resorption marker.

Results: In the reference group, BMD declined at the spine and hip ($P < 0.001$). In the randomized groups, hip BMD remained stable. Spine BMD increased in the zoledronate group and did not change in the alendronate group; at 12 months, the 2.2% difference between groups (95% confidence interval, 0.6 to 3.9%; $P = 0.009$) favored zoledronate. In heart transplant patients, spine BMD declined in the alendronate and increased in the zoledronate group (-3.0 vs. $+1.6\%$, respectively; between-group difference, 4.2%; 95% confidence interval, 2.1 to 6.3%; $P < 0.001$). In liver transplant patients, spine BMD increased comparably in both groups. Twelve-month C-telopeptide was lower in the zoledronate group than in the alendronate group (79 vs. 49%; $P = 0.04$).

Conclusions: One 5-mg infusion of zoledronate and weekly alendronate prevent bone loss at the hip and, in liver transplant patients, increase spine BMD. In heart transplant patients, spine bone BMD remained stable with zoledronate but decreased with alendronate. (*J Clin Endocrinol Metab* 97: 4481–4490, 2012)

Rapid bone loss is common during the first year after heart and liver transplantation (1–5). Vertebral fracture incidence ranges from 14 to 35% after heart (6–8) and 8 to 65% after liver transplantation, with recent stud-

ies showing lower rates (1–5). Several randomized trials (8–14) and our meta-analysis (15) demonstrate that bisphosphonates initiated immediately after transplantation prevent bone loss during the first year. Daily alendronate

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Abbreviations: BMD, Bone mineral density; CI, confidence interval; CTx, C-telopeptide; P1NP, N-terminal propeptides of procollagen type 1.

prevented bone loss after heart transplantation (8), and five iv infusions of zoledronate prevented bone loss after liver transplantation (9). Zoledronate is a long-acting bisphosphonate that increases bone mineral density (BMD) and reduces fracture incidence (16). In postmenopausal women, a single 5-mg infusion of zoledronate suppressed the bone resorption marker C-telopeptide (CTx) for 3 yr (17, 18), and in patients initiating glucocorticoids, it was associated with larger increases in BMD than daily oral risedronate (18). We hypothesized that either a single 5-mg infusion of zoledronate or weekly alendronate would prevent bone loss after heart or liver transplantation.

Patients and Methods

Design overview

In this 1-yr, double-placebo, double-masked study, patients were randomized to a single infusion of active zoledronate (5 mg), or active alendronate (70 mg weekly), or their matching placebos within 30 d of transplantation. Active alendronate or placebo was initiated the day after the infusion and continued for 12 months. The reference group included concurrently transplanted patients with T scores of -1.5 or greater; patients with T scores below -1.5 were eligible if they declined participation in the randomized study. Both randomized and reference groups received ergocalciferol (50,000 IU/d for 5 d) before randomization and calcium (945 mg) and vitamin D (1000 IU) daily after randomization.

Setting and participants

The study (www.Clinicaltrials.gov NCT00297830) was conducted in the Division of Endocrinology, the Irving Institute for Clinical and Translational Research and the Comprehensive Transplantation Center of Columbia University Medical Center (CUMC) with the approval of the Institutional Review Board. Written informed consent was obtained from all participants.

Men and women, aged 20 to 70 yr, who had undergone heart or liver transplantation at CUMC were eligible. Exclusion criteria were metabolic bone diseases, hypocalcemia, hypercalcemia, cancer (excepting atrial myxoma, hepatocellular carcinoma), thyrotoxicosis, serum creatinine above 2.0 mg/dl (176 μ mol/liter) by 1 month after transplantation, active peptic ulcer disease, inflammatory diseases, hormone replacement therapy, bisphosphonates, or calcitonin.

All received iv methylprednisolone intraoperatively and d 1, followed by oral prednisone and either cyclosporine or tacrolimus. Heart transplant participants received prednisone 100 mg tapering to 10 mg by 3 months, 5 mg by 6 months, and 1–5 mg at 12 months. Liver transplant participants received prednisone 20 mg, tapering to 5 mg by 3 months, and discontinuing at 6 months. Rejection was most commonly managed with glucocorticoids. Trough blood cyclosporine levels were maintained between 250 and 350 ng/ml for the first 6 months and between 100 and 250 ng/ml for the second 6 months. Trough blood tacrolimus levels were maintained between 6 and 12 ng/dl.

Randomization and interventions

Of 495 patients transplanted between March 2006 and July 2009, 235 were ineligible (Fig. 1); the most common reasons for ineligibility were age below 20 yr, serum creatinine levels above 2.0 mg/dl, or enrollment in another clinical trial. A total of 135 patients declined or were not approached. Eighty-four were randomized, 43 to alendronate and 41 to zoledronate. Two of 27 patients in the reference group died of transplant-related causes, and one withdrew before the 6-month visit. Thirty-five patients (81%) in the alendronate group and 37 (90%) in the zoledronate group completed 12 months of treatment. Eight withdrew from the alendronate group: four for patient preference, one for excessive bone loss at 6 months, and three for newly diagnosed neoplasms. In the zoledronate group, one patient died of sepsis and two withdrew (one with Guillain-Barre, one with sepsis) before the 6-month visit; one withdrew before the 12-month visit.

Outcomes and follow-up

BMD, spine radiographs, and fasting morning serum were obtained before randomization. BMD was repeated at 6 and 12 months, radiographs at 12 months, and serum at 2, 6, and 12 months. The primary efficacy variable was percentage change in total hip BMD. Primary safety endpoints included serum calcium and creatinine levels at 2, 6, and 12 months. Secondary outcomes included percentage change in BMD of the lumbar spine and femoral neck and serum CTx.

BMD was measured by dual-energy x-ray absorptiometry (QDR-4500 densitometer; Hologic, Inc., Bedford, MA); short-term *in vivo* coefficient of variation is 0.68% (spine) and 1.36% (femoral neck). T scores were generated using gender-specific databases provided by the manufacturer. Spine radiography was performed as described (19). Incident fractures were defined as a 20% or 4-mm decrease in any vertebral height (20). Serum was collected on the day of randomization, after the participants had received 5 d of ergocalciferol. Serum calcium, creatinine, and albumin were measured by autoanalyzer (Technicon Instruments, Tarrytown, NY). Serum was archived at -80°C for analysis of 25-hydroxyvitamin D and PTH, as previously described (8), and of CTx and N-terminal propeptides of procollagen type 1 (P1NP) by ELISA (IDS Ltd., Scottsdale, AZ).

Adverse events

Medications, side effects of study drugs, adverse events, clinical fractures, and compliance with alendronate/placebo were documented at each visit by interview and chart review. Non-vertebral fractures were ascertained by radiograph review. Gastrointestinal symptoms, common after transplantation, are also associated with alendronate (18). Gastrointestinal symptoms that resolved after discontinuation and recurred after resumption of alendronate were considered likely related to alendronate. If symptoms were intolerable, alendronate or matching placebo was discontinued, but the patient remained in the study.

Statistical analysis

The study was designed to test the two-sided superiority of zoledronate relative to alendronate and, secondarily, the one-sided superiority of zoledronate relative to the reference group. The primary outcome was the percentage change in total hip BMD at 12 months. Based on preliminary data that total hip BMD would decrease by $1.5 \pm 3.7\%$ on alendronate and in-

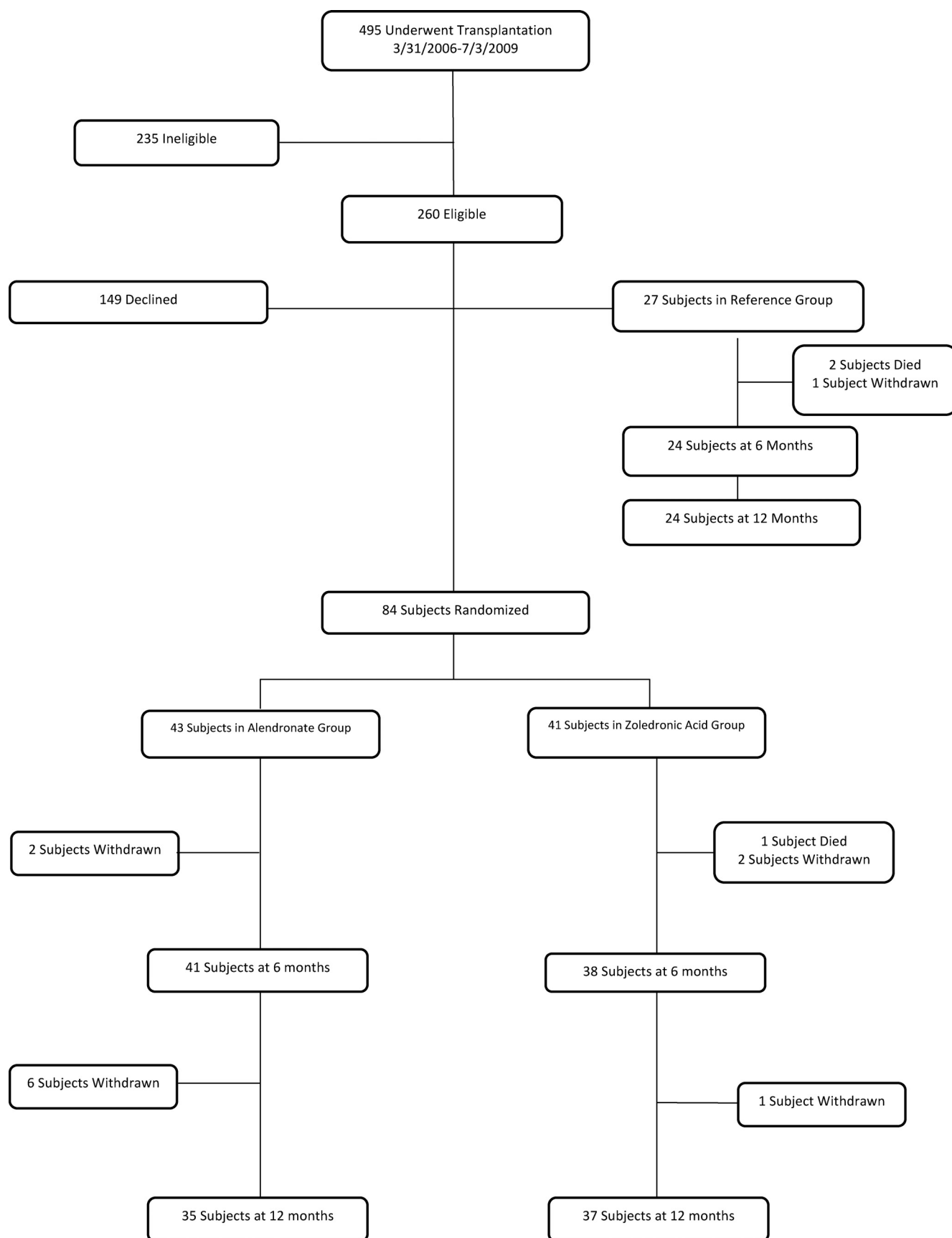


FIG. 1. Study profile.

crease by $1.0 \pm 3.7\%$ on zoledronate, we estimated that 35 subjects per group would provide 80% power and 5% α to detect a $2.5 \pm 3.7\%$ difference between randomized groups. Anticipating a 20% dropout, 84 subjects were randomized. The first 27 subjects who consented were enrolled as the reference group. Visits were coordinated with transplant appointments; minor timing variations were addressed by annualizing BMD changes. Data collected outside visit windows were treated as missing. No missing values were imputed.

Group differences at baseline were assessed with Student's *t* tests for continuous variables and χ^2 or Fisher's exact test for categorical variables. BMD percentage change from baseline was tested with linear mixed models for repeated measures; covariates were fixed effect of treatment (to test overall differences between treatments), interaction between treatment and time (to test for differences between the groups in percentage changes at 6 and 12 months), random effects of patient and error, and baseline BMD. The primary analysis compared BMD outcomes between the randomized groups. Separate models that controlled for age were constructed for secondary analyses comparing between-group differences between each randomized group and the reference group. Models were repeated separately for heart

and liver recipients. *Post hoc* comparison of between-group differences at specific follow-up times and within-group differences at different follow-up times were calculated from model estimated mean differences and SE of the differences using the method of simultaneous confidence limits. Group differences in biochemistries and immunosuppression were evaluated with linear mixed models as described above, except for serum calcium levels, which used a compound symmetry covariance structure. Differences in safety events between randomized groups were estimated with Fisher's exact test. All results are presented as means $\pm$ SE values and 95% confidence intervals (CIs). All hypotheses were tested by intention-to-treat. All analyses used SAS version 9.2 MIXED, FREQ, or TTEST procedures (SAS Institute, Cary, NC).

Results

Study population

Participants were predominantly male and white (Table 1). Randomized groups did not differ significantly by

TABLE 1. Baseline characteristics of study participants

Characteristic	Alendronate	Zoledronate	Reference	P values		
				A	B	C
Sample size (n)	43	41	27			
Heart transplant	26 (60)	27 (66)	17 (63)			
Liver transplant	17 (40)	14 (34)	10 (37)			
Days from transplantation to randomization	26 ± 7	27 ± 9	NA	0.65		
Age (yr)	54 ± 10	55 ± 8	48 ± 15	0.41	0.03	0.08
Gender						
Male	35 (81)	30 (73)	20 (74)	0.37	0.94	0.47
Female	8 (19)	11 (27)	7 (26)			
Postmenopausal	6 (75)	10 (91)	3 (43)	0.86	0.09	0.51
Race/ethnic group						
Non-Hispanic White	27 (63)	31 (76)	19 (70)	0.10	0.76	0.79
Non-Hispanic Black	4 (9)	6 (15)	3 (11)			
Hispanic	12 (28)	4 (9)	5 (19)			
Cardiac diagnosis						
Dilated	13 (50.0)	14 (51.9)	11 (64.7)	1.00	0.73	0.38
Ischemic	9 (34.6)	9 (33.3)	3 (17.6)			
Congenital	0 (0)	1 (3.7)	1 (5.9)			
Other	4 (15.4)	3 (11.1)	2 (11.8)			
Liver diagnosis						
Cholestatic	1 (5.9)	1 (7.2)	1 (10.0)	0.42	0.41	0.78
Viral	11 (64.7)	6 (42.8)	8 (80.0)			
Alcohol	3 (17.6)	1 (7.2)	0 (0)			
Other liver disease	1 (5.9)	3 (21.4)	1 (10.0)			
Viral and alcohol	1 (5.9)	3 (21.4)	0 (0)			
BMD (g/cm ²)						
Lumbar spine	0.976 ± 0.167	0.947 ± 0.113	1.111 ± 0.143	0.37	<0.001	<0.001
T score	-1.1 ± 1.5	-1.3 ± 1.0	0.1 ± 1.3	0.37	<0.001	<0.001
Z score	-0.5 ± 1.6	-0.6 ± 1.0	0.6 ± 1.4	0.69	<0.001	0.01
Femoral neck	0.790 ± 0.120	0.742 ± 0.113	0.912 ± 0.113	0.07	<0.001	<0.001
T score	-1.1 ± 0.8	-1.4 ± 0.8	-0.1 ± 0.9	0.08	<0.001	<0.001
Z score	-0.3 ± 0.9	-0.5 ± 0.7	0.5 ± 0.8	0.18	<0.001	0.01
Total hip	0.941 ± 0.136	0.904 ± 0.133	1.064 ± 0.122	0.22	<0.001	<0.001
T score	-0.6 ± 0.8	-0.9 ± 0.8	0.3 ± 0.8	0.23	<0.001	<0.001
Z score	-0.2 ± 0.9	-0.4 ± 0.8	0.6 ± 0.8	0.43	<0.001	0.01

Data are expressed as mean $\pm$ SD or number (percentage). NA, Not applicable. P values: A, Alendronate vs. zoledronate; B, zoledronate vs. reference; C, Alendronate vs. reference.

TABLE 2. Prednisone dose (mg/d)

Drug	Baseline	2 months	6 months	12 months	Comparisons		
					A	B	C
Heart and liver							
Alendronate	24.2 ± 1.2 ^a	10.9 ± 1.2	5.9 ± 1.2	3.6 ± 1.3	0.07	0.48	0.83
Zoledronate	17.8 ± 1.2 ^a	9.2 ± 1.3	5.1 ± 1.3	2.5 ± 1.3			
Reference	21.5 ± 2.0	10.1 ± 1.4	5.5 ± 1.3	3.8 ± 1.0			
Heart							
Alendronate	29.0 ± 1.7 ^a	14.1 ± 1.7	7.6 ± 1.7	5.8 ± 1.9	0.16	0.43	0.93
Zoledronate	20.9 ± 1.6 ^{a,b}	11.5 ± 1.7	6.3 ± 1.7	3.6 ± 1.8			
Reference	26.3 ± 2.6 ^b	12.8 ± 1.8	7.4 ± 1.7	5.5 ± 1.3			
Liver							
Alendronate	16.8 ± 1.0 ^a	6.0 ± 1.0	3.3 ± 1.0	0.3 ± 1.1	0.19	0.67	0.56
Zoledronate	13.6 ± 1.1 ^a	5.4 ± 1.1	3.3 ± 1.1	0.7 ± 1.1			
Reference	14.0 ± 1.0	4.7 ± 0.7	1.9 ± 0.6	0.3 ± 0.3			

Data are expressed as mean ± SE. **Boldface** data are statistically different from baseline within group. A *shared superscript* indicates a significant difference between the groups at that time-point. Comparisons: A, Alendronate vs. zoledronate group by time interaction; B, zoledronate vs. reference group by time interaction; C, alendronate vs. reference group by time interaction.

organ transplanted, days between transplantation and randomization, age, gender, menopausal status, race or ethnic group, type of heart or liver disease, or baseline BMD. Lumbar spine, femoral neck, or total hip T score was below −2.5 in 26% of the women and 20% of the men. The reference group was significantly younger than the zoledronate group, had proportionately fewer postmenopausal women than both randomized groups, although the differences were not significant, and had higher BMD than both randomized groups.

Immunosuppression

Prednisone dose was lower at randomization in the zoledronate group than the alendronate group, whether heart and liver transplant patients were considered together or separately (Table 2). By 2 months, prednisone doses were similar between groups, but they were higher in heart than liver transplant patients thereafter. At 12 months, most heart transplant patients were on prednisone (43 of 44; 99%), whereas most liver transplant patients were not (25 of 28; 89%). Cyclosporine doses declined comparably over 12 months in all three groups: by 42% in the alendronate group, 51% in the zoledronate group, and 41% in the reference group ($P = 0.04$; data not shown). Tacrolimus doses remained stable and did not differ among groups (data not shown). Neither cyclosporine nor tacrolimus doses differed by transplant.

Bone mineral density

In the reference group (Fig. 2), BMD declined by −2.2% at the total hip (95% CI, −3.6 to −0.7; $P < 0.001$), −3.3% at the femoral neck (95% CI, −4.8 to −1.8; $P < 0.001$), and −2.6% at the spine (95% CI, −4.4 to −0.9; $P < 0.001$). The amount and pattern of bone loss were similar in heart and liver patients (data not shown).

In the groups randomized to zoledronate or alendronate, total hip and femoral neck BMD did not change significantly from baseline (Fig. 2, A and B). In contrast, lumbar spine BMD increased significantly from baseline by 2.0% (95% CI, 0.6 to 3.4%) in the zoledronate group and did not change significantly (0.5%; 95% CI, −1.9 to 1.0%) in the alendronate group (Fig. 2C). At 12 months, the between-group differences were not significant at the total hip (0.5%; 95% CI, −0.7 to 1.7%; $P = 0.43$) or femoral neck (0.4%; 95% CI, −1.2 to 2.0%; $P = 0.62$). In contrast, the 2.2% between-group difference at the spine (95% CI, 0.6 to 3.9%; $P = 0.009$) was significant, favoring zoledronate.

Secondary analyses revealed greater total hip bone loss from baseline at 12 months in the reference than the zoledronate (estimated difference, 2.1%; 95% CI, 0.8 to 3.4%; $P = 0.002$) and alendronate groups (estimated difference, 1.6%; 95% CI, 0.1 to 3.2%; $P = 0.04$). Femoral neck bone loss was greater in the reference than the zoledronate (estimated difference, 2.4%; 95% CI, 0.6 to 4.3%; $P = 0.02$), but not the alendronate group (estimated difference, 1.7%; 95% CI, −0.2 to 3.6%; $P = 0.08$). Spine bone loss was greater in the reference group than the zoledronate group (estimated difference, 4.2%; 95% CI, 2.5 to 6.0%; $P < 0.001$), but not the alendronate group (estimated difference, 1.4%; 95% CI, −0.7 to 3.5%; $P = 0.18$).

Change in spine BMD differed by transplant type. In heart transplant patients (Fig. 2D), spine BMD increased by 1.6% in the zoledronate group (95% CI, −0.2 to 3.3%; $P = 0.08$) and decreased by 3.0% in the alendronate group (95% CI, −4.7 to −1.2%; $P = 0.001$). The between-group difference was 4.2% (95% CI, 2.1 to 6.3%; $P < 0.001$), favoring zoledronate. In liver transplant patients (Fig. 2E), spine BMD increased by 3.6% in the alendronate group (95% CI, 1.5 to 5.7%; $P = 0.017$) and 2.7%

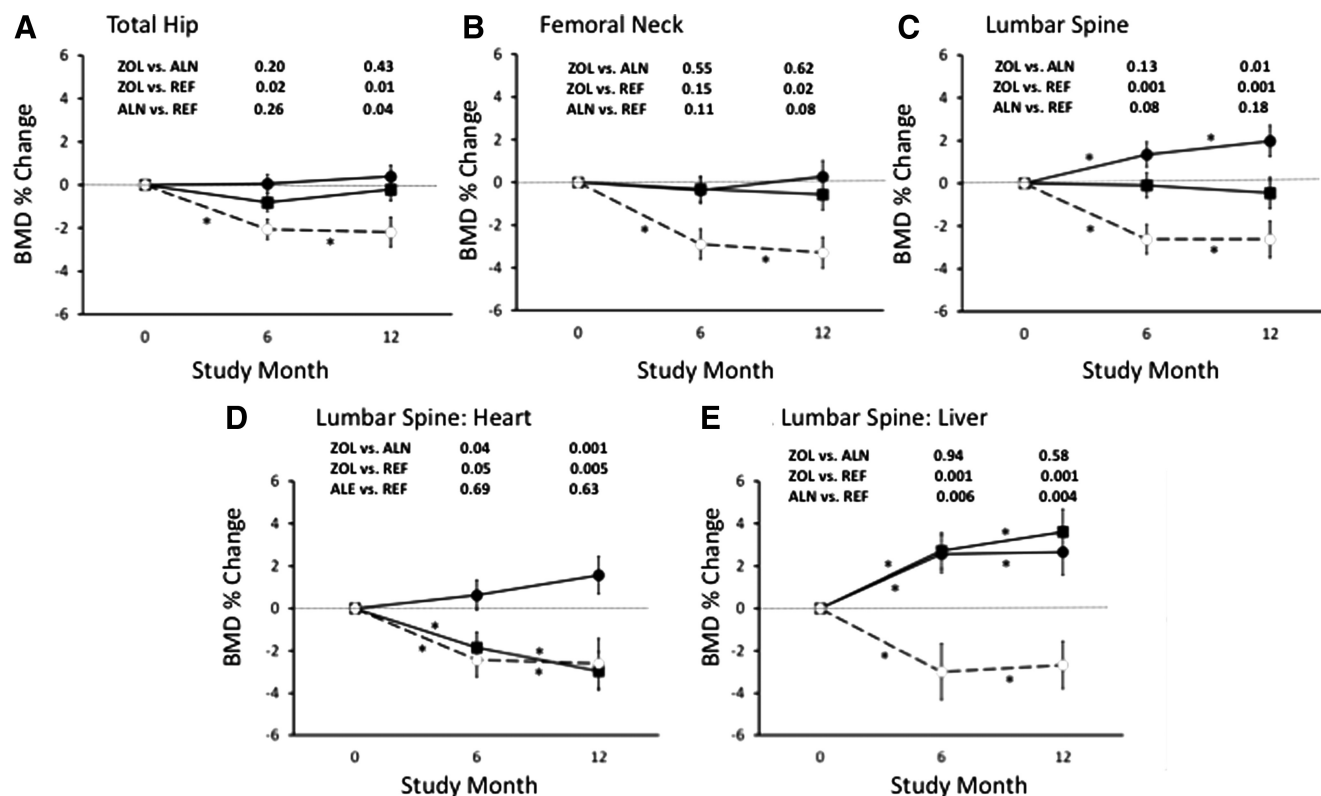


FIG. 2. Intention-to-treat analysis of mean ($\pm$ SE) percentage change in BMD. Asterisks, Significant differences from baseline; closed circles, zoledronic acid (ZOL); closed squares, alendronate (ALN); open circles, reference group (REF). A, Total hip (heart + liver); B, femoral neck (heart + liver); C, lumbar spine (heart + liver); D, lumbar spine: heart; E, lumbar spine: liver.

in the zoledronate group (95% CI, 0.5 to 4.8%; $P = 0.02$). The estimated between-group difference was -0.7% (95% CI, -3.2 to 1.8% ; $P = 0.58$). Heart and liver patients did not differ at the hip (data not shown).

Inclusion of prednisone dose at randomization and at later time points as a covariate in the analysis of BMD change did not affect the results either in the combined heart and liver transplant group analyses or in the separate heart and liver transplant group analyses.

Fractures

Paired spine radiographs were available for 33 patients in the zoledronate group, 36 patients in the alendronate group, and 21 patients in the reference group. Two patients in the alendronate group (5.6% of those with radiographs) and no patients in the zoledronate or reference groups sustained incident vertebral fractures. Nonvertebral fractures occurred in one patient in the zoledronate group, three in the alendronate group, and none in the reference group.

Biochemical indexes of mineral metabolism and bone remodeling

Mean serum calcium remained normal in all groups (Table 3). Serum creatinine was slightly higher at baseline in the reference group and remained stable, whereas there were slight but significant increases in the randomized

groups. Serum 25-hydroxyvitamin D did not change. Serum PTH increased significantly from baseline in the zoledronate and alendronate groups and remained stable in the reference group. There were no differences between heart and liver transplant patients (data not shown).

By 2 months, serum CTx decreased by 43% in the alendronate and 70% in the zoledronate group (Fig. 3A). At 12 months, serum CTx, expressed as percentage change from baseline, was significantly lower in the zoledronate than the alendronate group. In heart transplant patients, serum CTx tended to decline more in those randomized to zoledronate than alendronate (80 vs. 47%; $P = 0.06$). Serum P1NP followed a similar pattern. At 12 months, CTx was significantly lower in heart transplant patients who received zoledronate than the reference group (0.15 ± 0.22 vs. 0.51 ± 0.07 pg/ml, respectively; $P < 0.001$), whereas those who received alendronate did not differ from the reference group (0.35 ± 0.23 vs. 0.51 ± 0.07 pg/ml, respectively; $P = 0.26$; Fig. 3B). In liver transplant patients, serum CTx and P1NP did not change in any group.

Compliance and adverse events

In terms of compliance, 91% of the randomized subjects took more than 80% of dispensed doses of alendronate or its matching placebo. Transplantation-associated adverse events did not differ among the groups (Supple-

TABLE 3. Biochemistries

Analyte	Randomization	2 Months	6 Months	12 Months	Comparisons		
					A	B	C
Calcium							
Alendronate	9.1 ± 0.3 ^a	8.8 ± 0.2	9.2 ± 0.1	9.6 ± 0.4	0.03	0.29	0.12
Zoledronate	8.9 ± 0.3	9.1 ± 0.2	9.4 ± 0.1 ^a	9.6 ± 0.4			
Reference	9.0 ± 0.1 ^a	9.0 ± 0.1	8.8 ± 0.1 ^a	8.9 ± 0.2			
Creatinine							
Alendronate	0.8 ± 0.1	1.1 ± 0.1	1.3 ± 0.1	1.7 ± 0.2	0.68	0.60	0.58
Zoledronate	0.8 ± 0.1	1.0 ± 0.1	1.2 ± 0.1	1.5 ± 0.2			
Reference	1.1 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.2 ± 0.1			
25-hydroxyvitamin D							
Alendronate	37 ± 5 ^a	32 ± 3	39 ± 2	50 ± 7	0.80	0.87	0.78
Zoledronate	31 ± 5 ^a	27 ± 3 ^a	37 ± 2	46 ± 7 ^a			
Reference	43 ± 3	38 ± 3 ^a	41 ± 3	46 ± 4 ^a			
PTH							
Alendronate	12 ± 12	35 ± 7^a	42 ± 6	65 ± 17	0.46	0.40	0.21
Zoledronate	19 ± 12	38 ± 7^b	43 ± 6	57 ± 16			
Reference	28 ± 3	31 ± 3 ^{a,b}	31 ± 3	32 ± 3			
Serum CTx							
Alendronate	0.68 ± 0.12	0.40 ± 0.07^a	0.30 ± 0.06^a	0.21 ± 0.18	0.001	0.001	0.65
Zoledronate	0.78 ± 0.12	0.22 ± 0.08^{a,b}	0.22 ± 0.06^b	0.07 ± 0.17^a			
Reference	0.64 ± 0.06	0.51 ± 0.07^b	0.50 ± 0.06 ^{a,b}	0.48 ± 0.06 ^a			
Serum P1NP							
Alendronate	55.1 ± 5.4	43.2 ± 5.4	54.7 ± 8.2	42.3 ± 4.6 ^a	0.51	0.001	0.007
Zoledronate	55.3 ± 4.2	37.8 ± 3.6	41.6 ± 6.4^a	42.6 ± 6.6 ^b			
Reference	45.4 ± 4.9	48.2 ± 5.5	61.5 ± 7.1 ^a	74.4 ± 7.5 ^{a,b}			

Data are expressed as mean ± SE. **Boldface** data are statistically different from baseline within group. A *shared superscript* indicates a significant difference between the groups at that time-point. Comparisons: A, Alendronate vs. zoledronate group by time interaction; B, zoledronate vs. reference group by time interaction; C, alendronate vs. reference group by time interaction.

mental Table 1, published on The Endocrine Society's Journals Online web site at <http://jcem.endojournals.org>). There was no difference between the two intervention groups in gastrointestinal symptoms, serum creatinine, serum creatinine levels over 3.0 mg/dl, hypocalcemia, postinfusion flu-like symptoms, or arrhythmias. More patients in the alendronate group (n = 7) than the zoledronic acid group (n = 1) experienced increases in serum creatinine above 2.0 mg/dl, but the difference was not statistically significant ($P = 0.09$). In three patients, the increase was transient, most commonly associated with sepsis. Of the five patients in whom the serum creatinine remained

above 2.0 mg/dl, one had biopsy-proven nephropathy related to hepatitis C infection and diabetes; one developed primary hyperparathyroidism, hypercalciuria, and dehydration; one with a baseline serum creatinine of 2.0 mg/dl later developed sepsis and dehydration; one developed cellulitis and urosepsis; and one had no apparent etiology other than cyclosporine A toxicity.

Discussion

We compared a single 5-mg infusion of zoledronate with 12 months of weekly oral alendronate for prevention of

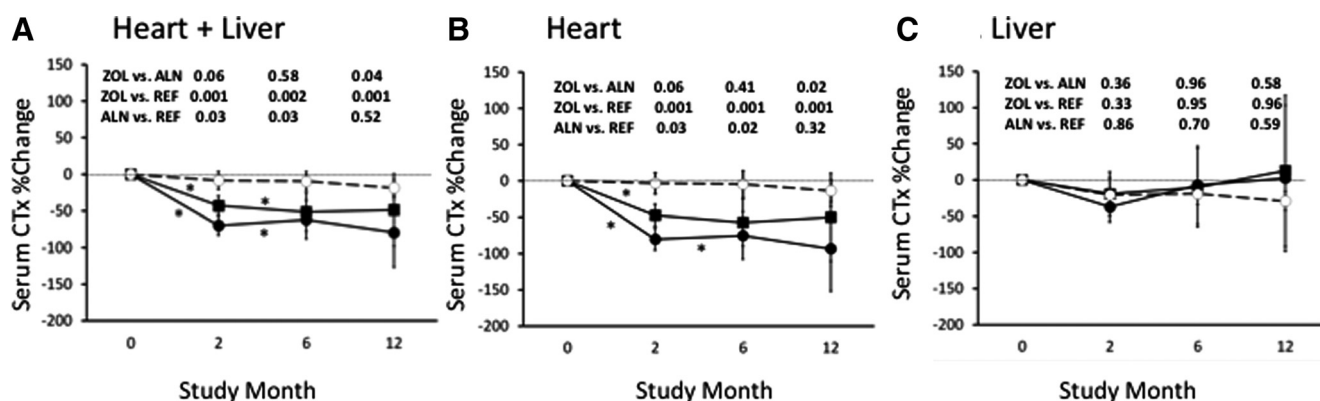


FIG. 3. Mean (±SE) percentage change in serum CTx. Asterisks, Significant differences from baseline; closed circles, zoledronic acid (ZOL); closed squares, alendronate (ALN); open circles, reference group (REF). A, Heart + liver; B, heart; C, liver.

bone loss during the first year after heart or liver transplantation. The primary analysis revealed no bone loss at the total hip and femoral neck with either intervention. At the spine, however, there was a significant 2.2% between-group difference at 12 months that favored zoledronate. Secondary analyses revealed that this was limited to heart transplant patients, in whom spine BMD declined in the alendronate group and remained stable in the zoledronate group. In contrast, spine BMD increased comparably and significantly in liver transplant patients treated with both drugs. The reference group sustained significant bone loss at all sites. The zoledronate group sustained less bone loss at all sites than the reference group, whereas the alendronate group sustained less bone loss than the reference group only at the total hip. These results suggest that a single infusion of zoledronate prevents bone loss at the femoral neck and total hip and improves spine BMD in both heart and liver transplant recipients. In contrast, weekly alendronate prevents bone loss at the total hip and femoral neck in heart and liver transplant recipients, but is associated with significant spine bone loss in heart transplant recipients, and increases spine BMD only in liver transplant recipients.

Previous studies of posttransplantation bone loss suggest that it is related to concomitant therapy with high-dose glucocorticoids and calcineurin inhibitors (15, 21) and associated with biochemical evidence of uncoupled bone remodeling, with decreased formation and increased resorption markers (9, 22, 23). As prednisone doses decrease, bone formation recovers, and rates of bone loss diminish (23). This transient uncoupling of bone remodeling is associated with relatively rapid bone loss during the first 6 months, after which BMD declines less rapidly, stabilizes, or improves (8, 23–25).

Oral bisphosphonates reduce rates of bone loss and fracture in glucocorticoid-induced osteoporosis (18, 26–28), likely by suppressing bone resorption. In heart transplant patients randomized to daily alendronate, spine BMD remained stable despite small but significant decreases at the total hip (1.5%) and femoral neck (1.7%) (8). In liver transplant patients randomized to weekly alendronate (29), BMD increased by 5.1% at the spine and 3.6% at the femoral neck, larger increases than observed in our study (3.5% at the spine, 0.1% at the femoral neck). Although gender, baseline BMD, and prednisone doses were similar to our study, their patients were younger and received concurrent calcitriol 0.5 μ g daily. Alendronate also prevents bone loss immediately after kidney transplantation (30) and improves BMD in long-term kidney transplant recipients (31, 32).

Intravenous bisphosphonates have also been studied after organ transplantation. In male heart transplant re-

cipients randomized to quarterly ibandronate or placebo, BMD remained stable in the ibandronate group and fell by 23–25% in the control group (12). Incident vertebral fractures were significantly lower in the ibandronate group than the control group (13 vs. 53%, respectively) (12). However, glucocorticoid doses were much higher than in our study. Quarterly ibandronate infusions also prevented bone loss and reduced vertebral fractures after kidney transplantation (13). Crawford *et al.* (9) randomized liver transplant patients to placebo or a much higher dose of zoledronate than we used: 4 mg at 1 wk and at 1, 3, 6, and 9 months after transplantation. Rates of bone loss were significantly lower in the zoledronate group. In another randomized study, patients who received eight infusions of zoledronate (4 mg) during the first year after liver transplantation had significantly less bone loss and fewer vertebral fractures (8.5 vs. 22.5%) (33).

When liver and heart transplants were analyzed together, zoledronate lowered bone turnover markers to a greater extent and for a longer period than alendronate. However, this was limited to heart transplant recipients. CTx did not decrease significantly in our liver transplant recipients treated with zoledronate and alendronate for reasons that are unclear. However, although the decline in CTx in our liver transplant patients was not significant, it was comparable to the decline in deoxypyridinoline observed by Crawford *et al.* (9). Bodingbauer *et al.* (33) also found no decline in resorption markers after liver transplantation, despite high doses of zoledronate. Despite the lack of decline in CTx in our liver transplant recipients, however, they experienced comparable increases in spine and maintenance of hip BMD, whereas BMD declined at all sites in untreated patients. In heart transplant patients, less potent suppression of bone resorption by alendronate than zoledronate provided less benefit at the spine. The differing response to alendronate at the lumbar spine in heart and liver transplant patients may have been related to less prednisone exposure at randomization and thereafter in the latter.

Alendronate and zoledronate were well tolerated and appeared safe. Mild postinfusion hypocalcemia and flu-like symptoms occurred in more patients in the zoledronate group than the alendronate group, but the differences were not significant. Mild deterioration in renal function affected both randomized groups comparably, and to an extent similar to that commonly seen after organ transplantation (34, 35). Serum creatinine exceeded 2.0 mg/dl at some point during the first posttransplant year in seven patients in the alendronate group and one in the zoledronic acid group; in three, the increase was transient, and in four it stabilized between 2.0 and 3.0 mg/dl; and one patient developed worsening diabetic and hepatitis C-re-

lated nephropathy that necessitated kidney transplantation. In all, there was a known etiology of declining renal function. Gastrointestinal side effects and incidence of atrial fibrillation did not differ.

This study has several limitations. We did not include a randomized untreated group because we believed that high fracture rates reported in untreated patients required an active comparator design. The reference group was younger and had higher BMD than the randomized groups. However, we controlled analyses for baseline BMD and age, and we believe the data provide a benchmark for interpreting the effects of the interventions. The study was conducted in a single institution, and results may not apply to other centers. Heart and liver transplant recipients differ in terms of pretransplant bone disease (usually high bone turnover in heart failure and low bone turnover in liver failure) and exposure to prednisone. However, as rates and patterns of bone loss were comparable in untreated heart and liver transplant patients, this heterogeneity may broaden generalizability of the results. Because vitamin D deficiency is common in transplant recipients (36) and has been associated with profound hypocalcemia after zoledronate (37), we administered ergocalciferol to all randomized and reference participants without a history of nephrolithiasis; this may have resulted in less bone loss than prior studies. Fracture rates were also lower than previously reported (8, 9), and there were none in the reference group, likely related to their higher BMD and lower age. Moreover, the study was not powered to detect differences in fracture rates, an important clinical outcome but one that would require a large comparative effectiveness trial. Thus, it is unclear whether the two interventions differ enough to make global recommendations based upon this outcome, particularly because alendronate is available as a generic and less expensive treatment than zoledronate.

In summary, a single 5-mg infusion of zoledronate, a much smaller dose than used in prior studies, and 12 months of weekly alendronate prevented bone loss at the hip during the first year after heart and liver transplantation. At the spine, there was a significant 2.2% between-group difference, favoring zoledronate. When the type of organ transplant was considered, zoledronate and alendronate were associated with comparable improvements in liver transplant patients, but zoledronate was superior to alendronate in heart transplant patients. The biological relevance of the overall 2.2% difference in lumbar spine bone loss between the zoledronate and alendronate groups may depend upon the condition of the patient at the time of transplantation. For the 26% of women and 20% of men who already had osteoporosis at baseline in our study, for those with T scores below -1.5 who are of

necessity embarking upon a course of glucocorticoid therapy, and others who are at high risk of fracture (postmenopausal women, those with a prior osteoporotic fracture), a further loss of 2.2%, particularly when it occurs over a relatively short period of time (6 months), might have considerable impact. Such patients may benefit from a more aggressive approach (zoledronate in this case). In contrast, for patients with relatively normal BMD or those at low risk of fracture, a 2.2% loss might not have serious consequences. In addition, the medication burden is high in most transplant recipients, and a single dose of zoledronate may be easier to comply with than weekly alendronate. Thus, the demonstration that a single 5-mg infusion of zoledronate lowers serum markers of bone resorption and prevents bone loss at all sites during the first posttransplant year should be of interest to organ transplantation programs.

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