Alendronate Prevents Bone Loss in Patients with Acute Spinal Cord Injury: A Randomized, Double-Blind, Placebo-Controlled Study


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Context: Patients who sustain an acute spinal cord injury (SCI) experience rapid dramatic reductions in bone mineral density (BMD), especially marked in sublesional areas and sometimes leading to hypercalcemia and hypercalciuria, as well as increased fracture risk.

Objective: In this prospective, double-blind, randomized, placebo-controlled study, we evaluated the hypothesis that oral alendronate administration would preserve BMD when administered soon after acute SCI.

Patients and Intervention: Thirty-one patients with acute SCI were randomly allocated to receive oral alendronate 70 mg/wk or placebo, within 10 d of acute SCI, for 12 months.

Main Outcome Measurements: At entry and at 3, 6, 12, and 18 months, total body bone density, lumbar and hip BMD, ultrasound of the calcaneus, 24-h urinary calcium, and serum C-telopeptide (βCTX) were measured.

Results: At study entry, patients in the two groups were well matched for age, gender, severity of neurological deficit, BMD, urinary calcium, and βCTX. BMD indices declined steadily in the placebo group, and this effect was attenuated significantly by alendronate. After 12 months, there was a 5.3% difference (P < 0.001) in total body BMD and a 17.6% difference (P < 0.001) in the total hip BMD between the two groups. Alendronate compared with placebo induced significant (P < 0.001) reductions in urinary calcium excretion and serum βCTX. No treatment-related side effects were noted.

Conclusions: We conclude that alendronate therapy, 70 mg/wk, initiated soon after acute SCI, prevents bone loss and is not associated with side effects. (J Clin Endocrinol Metab 92: 1385–1390, 2007)

Spinal cord injury (SCI) affects 28.5–40 subjects per 1 million people in first-world countries (1, 2). Bone loss after SCI occurs rapidly below the level of the lesion (3, 4) as the result of increased bone resorption and impaired bone formation (5, 6), thereby predisposing to hypercalcemia, hypercalciuria, renal calculi, osteoporosis, and fracture (7). Bone loss in sublesional areas can be as high as 4% per month in trabecular bone and 2% per month in cortical bone (8). Loss of bone peaks 3–5 months after SCI but is ongoing for approximately 2 yr before reaching a new steady state (5, 6). The neurological level of SCI determines the extent but not the degree of bone loss with greater bone loss being observed in tetraplegia and complete spinal cord lesions (9, 10). Attempts to prevent bone loss using rehabilitation orientated approaches such as standing, orthotically aided walking, physical exercise, functional electrical stimulation, and low-intensity ultrasound have proved disappointing (6).

Pharmacological interventions hitherto have focused on reversing bone resorption. Calcitonin in varying doses and methods of administration has given variable results in paraplegia (11). Likewise, the outcome using bisphosphonates has been variable. Etidronate produced long-term benefit in lower limb bone mineral density (BMD) in selected walking SCI patients (12), whereas tiludronate appeared effective in reducing bone resorption and preserving bone mass in a histomorphometric study in 20 paraplegic patients (13). Intravenous pamidronate has been shown to attenuate bone loss in SCI (14) and normalize serum calcium in immobilization hypercalcemia (15). The aminobisphosphonate, alendronate (1000 times more potent than etidronate), in an open observational study, reversed BMD loss in men with established SCI (16), increased both axial and trabecular bone density while reducing the risk of vertebral and hip fractures in postmenopausal women (17), and has proven efficacy and safety in men treated for osteoporosis (18). Alendronate also prevents hypercalciuria and bone loss after bed rest (19) and lower leg fracture (20). The efficacy and tolerability of alendronate, 70 mg once weekly, has recently been demonstrated in postmenopausal women with osteoporosis (21). To our awareness, however, no studies have assessed objectively the efficacy and safety of alendronate administered for a sustained period from the time of acute SCI.

The aim of this study was to test the hypothesis that alendronate 70 mg once weekly, administered for 12 months,
would prevent loss of bone mass in patients with acute SCI without exhibiting serious side effects.

Subjects and Methods

Study design and subjects

Between March 2001 and February 2004, patients aged between 17 and 55 yr presenting to the Burwood Hospital Spinal Injury Unit, Christchurch, New Zealand, with acute SCI [C4–L4; American Spinal Cord Association grading system for severity of neurological deficit after acute SCI (ASIA), A–D] were approached to enter a prospective, double-blind, placebo-controlled study to determine the efficacy and safety of oral alendronate. Patients were assigned to active oral alendronate or placebo within 10 d of acute SCI. Once weekly they took alendronate 70 mg or matched placebo with water within a period of 30 min while sitting upright and after overnight fasting. No supplement of dietary calcium was taken, but vitamin D was administered to those with low baseline serum vitamin D levels (25-hydroxyvitamin D < 50 nmol/liter). Treatment with alendronate and matched placebo was continued for 12 months, and patients were reviewed finally 6 months after cessation of therapy. The study was approved by the Canterbury Ethics Committee.

Measurements

Data including body weight, height, body mass index, biochemistry and urine indices, BMD, SCI (ASIA) score, and level of mobility were collected in all subjects at baseline and at 3, 6, 12, and 18 months after acute SCI. BMD of the lumbar spine, first to fourth lumbar vertebrae, total hip, femoral neck, trochanter, and total body (BMD, fat mass, and lean body mass) were measured using dual x-ray absorptiometry (DPX-NT; Lunar, Madison, WI). Ultrasound of the nondominant heel, speed of sound, broadband ultrasound attenuation, and derived stiffness were measured using Achilles Plus Solo (Lunar). Bone density was expressed as grams per square centimeter and ultrasound values as dBMHz (frequency times intensity) and quality index. The sound attenuation, and derived stiffness were measured using Achilles Plus Solo (Lunar). Bone density was expressed as grams per square centimeter and ultrasound values as dBMHz (frequency times intensity) and quality index. These latter two patients did not alter the significance of differences between the two groups for any of the measured variables. In six patients, complete measurement of bone density at the lumbar spine (L1–L4) was not possible because of metal implants (alendronate, three patients; placebo, three patients), and no spinal dual x-ray absorptiometry data were available in one patient due to placement of metal implants between L1 and L4. Neurological deficit according to the ASIA grading scale in the alendronate group identified nine subjects ASIA-A at entry and completion, one ASIA-A at entry and ASIA-B at completion, and one ASIA-B at entry and ASIA-D at completion. Three had ASIA-C at entry, and three had ASIA-D at completion. In the placebo group, there were 12 with ASIA-A at entry, eight with ASIA-A at completion, one with ASIA-B, and two with ASIA-D at completion. Four had ASIA-B at entry; one remained at ASIA-B, one had ASIA-C, and two had ASIA-D at completion. The remaining patient that entered at ASIA-D and completed at ASIA-D. The ASIA grading scale is as follows: A, complete: no motor or sensory function is preserved in the sacral segments S4–S5; B, incomplete: sensory but not motor function is preserved below the neurological level and includes the sacral segments S4–S5; C, incomplete: motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3; D, incomplete: motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more; and E, normal: motor and sensory function are normal.

Results

Subject characteristics and adherence

Thirty-one patients entered the study. Fifteen (10 males and five females) were randomized to alendronate and 16 (12 males and four females) to placebo. All females were premenopausal, and none had any preexisting menstrual abnormalities. No significant differences in mobility were noted at randomization between the groups. There were no statistically significant differences in body weight (79.1 ± 4.4 vs. 74.3 ± 4.1 kg) or body mass index (26.4 ± 1.1 vs. 24.5 ± 1) between alendronate and placebo groups at baseline or at 18 months (weight, 76.0 ± 5.2 vs. 74.1 ± 4.8 kg; body mass index, 25.1 ± 1.3 vs. 24.5 ± 12). In the alendronate group, nine patients had cervical cord injuries, one had thoracic injury, and five had thoraco-lumbar injuries. In the placebo group, six subjects had cervical cord injuries, five had thoracic injuries, and five had thoraco-lumbar injuries. Six patients (three from each group) did not complete the study, and their data were not included in the analyses: four due to noncompliance and two in the placebo group because of inability to attend visits at 18 months. Inclusion of 12-month data from these latter two patients did not alter the significance of differences between the two groups for any of the measured variables.

Adverse events and compliance

All side effects and adverse events were noted and graded according to the neurological level and at least half of key muscles below the neurological level have a muscle grade of 3 or more; and E, normal: motor and sensory function are normal.

Statistical analysis

Power calculations based on Nance et al. (14) indicated that a sample size of 15 in each group would give us sufficient statistical power (>80%) to show a difference in bone loss of 7% per year or more between treatments as statistically significant (two-tail α = 0.05). Subjects were prospectively randomized in predetermined blocks of six by a blinded observer (C.M.F.). Baseline variables were compared between treatment arms using the t test or Fisher’s exact test and independent t tests as appropriate. Changes in outcome measures were compared between active and placebo treatments over time using repeated-measures ANOVA. Adverse event rates were compared using χ² tests. Data are presented as mean ± SEM.

TABLE 1. Mobility status of all subjects at 18 months

<table>
<thead>
<tr>
<th>Mobility status</th>
<th>ALN</th>
<th>PLAC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheelchair</td>
<td>8</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>Wheelchair and assisted walking</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Walking</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>16</td>
<td>31</td>
</tr>
</tbody>
</table>

ALN, Alendronate; PLAC, placebo.
Patient mobility at study completion is shown in Table 1. There was no difference in the level of mobility and independence between the two groups. No renal calculi were detected in any subject, and heterotropic calcification was observed in only one patient (placebo group).

Alendronate-induced changes in BMD and bone turnover
Statistically significant changes across 18 months were noted between alendronate and placebo groups for five of the six total body measures (Fig. 1 and Table 2). No significant differences in bone loss were observed between men and women.

**TABLE 2.** Baseline T-scores and absolute values and BMD changes over 18 months according to treatment group

<table>
<thead>
<tr>
<th>T-score</th>
<th>Month 0</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 12</th>
<th>Month 18 (0–12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS ALN</td>
<td>-0.06</td>
<td>1.196</td>
<td>0.050</td>
<td>1.217</td>
<td>0.052</td>
</tr>
<tr>
<td>P</td>
<td>-0.33</td>
<td>1.178</td>
<td>0.048</td>
<td>1.172</td>
<td>0.050</td>
</tr>
<tr>
<td>T hip ALN</td>
<td>0.42</td>
<td>1.108</td>
<td>0.254</td>
<td>1.106</td>
<td>0.058</td>
</tr>
<tr>
<td>P</td>
<td>0.77</td>
<td>1.154</td>
<td>0.050</td>
<td>1.081</td>
<td>0.054</td>
</tr>
<tr>
<td>F neck ALN</td>
<td>0.47</td>
<td>1.090</td>
<td>0.055</td>
<td>1.092</td>
<td>0.059</td>
</tr>
<tr>
<td>P</td>
<td>0.76</td>
<td>1.143</td>
<td>0.051</td>
<td>1.091</td>
<td>0.054</td>
</tr>
<tr>
<td>Troch ALN</td>
<td>0.53</td>
<td>0.930</td>
<td>0.051</td>
<td>0.923</td>
<td>0.055</td>
</tr>
<tr>
<td>P</td>
<td>0.77</td>
<td>0.977</td>
<td>0.047</td>
<td>0.893</td>
<td>0.051</td>
</tr>
<tr>
<td>Shaft ALN</td>
<td>1.307</td>
<td>0.065</td>
<td>1.303</td>
<td>0.068</td>
<td>1.276</td>
</tr>
<tr>
<td>P</td>
<td>1.335</td>
<td>0.060</td>
<td>1.260</td>
<td>0.063</td>
<td>1.155</td>
</tr>
<tr>
<td>TB ALN</td>
<td>1.271</td>
<td>0.038</td>
<td>1.271</td>
<td>0.040</td>
<td>1.272</td>
</tr>
<tr>
<td>P</td>
<td>1.269</td>
<td>0.036</td>
<td>1.244</td>
<td>0.037</td>
<td>1.226</td>
</tr>
<tr>
<td>TB arms ALN</td>
<td>0.975</td>
<td>0.046</td>
<td>1.014</td>
<td>0.046</td>
<td>1.010</td>
</tr>
<tr>
<td>P</td>
<td>1.017</td>
<td>0.043</td>
<td>0.987</td>
<td>0.042</td>
<td>0.986</td>
</tr>
<tr>
<td>TB legs ALN</td>
<td>1.364</td>
<td>0.053</td>
<td>1.351</td>
<td>0.058</td>
<td>1.327</td>
</tr>
<tr>
<td>P</td>
<td>1.408</td>
<td>0.046</td>
<td>1.365</td>
<td>0.054</td>
<td>1.300</td>
</tr>
</tbody>
</table>

Values are mean ± (SEM). ALN, Alendronate; F, femoral; LS, lumbar spine; P, placebo; Shaft, femoral shaft; T, total; TB, total body; Troch, trochanter.
women. At 12 months, preservation of bone density occurred in the alendronate group compared with the placebo group at total body (−0.4 ± 1.2% vs. −5.7 ± 0.9%; \( P < 0.001 \)) and pelvic sites (−1.4 ± 1.6% vs. −16.6 ± 1.6%; \( P < 0.001 \)), total body trunk (1.7 ± 1.4% vs. −5.4 ± 0.9%; \( P < 0.001 \)), and total body legs (−5.6 ± 1.1% vs. −12.7 ± 1.4%; \( P < 0.001 \)).

All four sites at the hip showed statistically significant “advantages” in BMD for alendronate vs. placebo at 12 and 18 months (Fig. 2 and Table 2). These included preservation over 12 months of femoral neck BMD (0.3 ± 1.0% vs. −16.4 ± 2.0%; \( P < 0.001 \)) and less BMD loss at the total hip (−3.3 ± 0.9% vs. −20.9 ± 1.9%; \( P < 0.001 \)), trochanter (4.5 ± 1.5% vs. −26.3 ± 2.4%; \( P < 0.001 \)), and femoral shaft (−3.8 ± 1.1% vs. −19.0 ± 2.0%; \( P < 0.001 \)). Increases in BMD of the spine (>4%, not significant) were also noted in those receiving alendronate, with no change occurring in the placebo group.

Ultrasound values declined in both groups with only speed of sound (−3.2 ± 0.8% vs. −5.9 ± 0.8%; \( P = 0.039 \)) showing a statistically significant difference between groups. Measurements of body composition using DPX-NT showed no differences between the groups at 12 months. Fat mass increased similarly in the two groups (27,465 ± 3,116 g vs. 23,848 ± 2,885 g, not significant) and was not significantly different 6 months after discontinuation of treatment (27,107 ± 3,911 g vs. 25,062 ± 3,621, not significant). Lean body mass at baseline, 12 months, and 6 months after discontinuation was not significantly different between groups but had decreased in both groups by 12–14% (data not shown).
shown). Twenty-four-hour urinary calcium excretion was initially high in both groups (6.79 ± 0.9 in the alendronate group vs. 8.78 ± 0.8 mmol/liter in the placebo group, not significant) but had decreased significantly in the alendronate group at 3 months (2.66 ± 1.032 vs. 9.13 ± 0.91 mmol/liter; P < 0.001) and was still significantly less than the placebo group at 18 months (2.89 ± 0.074 vs. 3.9 ± 0.65 mmol/liter; P < 0.001) (Fig. 3). Plasma βCTX levels were high in both groups at baseline (0.89 ± 0.15 nmol/g alendronate vs. 1.07 ± 0.14 nmol/g placebo, not significant) but had decreased to normal levels in the alendronate group at 3 months compared with continuing high values in the placebo group (0.50 ± 0.12 vs. 1.02 ± 0.11 nmol/g; P < 0.001). Values were not different between the two groups 6 months after completion of alendronate and placebo administration (Fig. 3).

Other analyses

Six patients (three taking alendronate and three in the placebo group) had low serum 25-hydroxyvitamin D levels initially high in both groups (6–43 nmol/liter) and received vitamin D supplementation (calcitriol 0.25 mg twice daily in three subjects; calciferol forte 50,000 IU, five tablets orally, followed by one tablet monthly in three subjects). No differences between the groups were noted in serum calcium (2.27 ± 0.037 alendronate vs. 2.26 ± 0.034 mmol/liter placebo, not significant), phosphate (1.25 ± 0.074 vs. 1.22 ± 0.068 mmol/liter, not significant), or alkaline phosphatase (135.6 ± 21.8 vs. 143.5 ± 20.22 IU/liter, not significant) at baseline. At 12 months, serum calcium levels were similar in the two groups and were unaltered from baseline (2.28 ± 0.03 vs. 2.30 ± 0.032 mmol/liter, not significant), whereas both serum phosphate (0.97 ± 0.041 vs. 0.99 ± 0.038 mmol/liter, not significant) and alkaline phosphatase (66.7 ± 8 vs. 79.1 ± 7.4 nmol/liter IU/liter, not significant) were similar in the two groups having returned to normal levels.

Adverse events

There were no significant differences between alendronate and placebo groups regarding reported abdominal pain (eight vs. five), constipation (three vs. seven), diarrhea (four vs. two), dyspepsia (zero vs. three), nausea (11 vs. 14), or vomiting (one vs. five). Ten serious “adverse events” were noted in six subjects in the alendronate group (one urinary tract infection, six surgical procedures, two tendon contrac-

tures, and one pressure area). Ten serious adverse events occurred in five subjects in the placebo group (four surgical procedures, three hypertonia, three syringomyelia). A large number of minor adverse events were observed, but no difference was noted between the alendronate (n = 311) and placebo groups (n = 368).

Discussion

Acute SCI precipitates rapid bone loss below the level of the lesion due to dramatic increases in bone resorption and impaired bone formation (5), leading frequently to hypercalcemia, hypercalciuria, renal calculi, osteoporosis, and fragility fractures. On the basis that alendronate is demonstrably effective in reversing bone loss in men with established SCI (16), increases bone density in men with osteoporosis, and prevents hypercalciuria and bone loss after lower leg fracture and bed rest (19, 20), we hypothesized that this drug would prevent bone loss when administered soon after SCI. To address this hypothesis, we randomized patients to receive 12 months of alendronate or placebo, within 10 d of acute SCI.

Bone loss in sublesional sites after SCI has been well described, with the magnitude observed in our placebo group being similar to that reported from observational and prospective studies (3, 9, 22). The major finding in our study is that alendronate given for 12 months, starting soon after acute SCI, without calcium supplementation or routine vitamin D, proved superior to placebo in preventing bone loss. This was so for total body bone loss and also regionally. Changes in BMD at the spine are similar to data reported in men with established SCI treated with 10 mg alendronate daily for 24 months (16). The spine does not tend to lose BMD after SCI (9, 10, 14, 23), irrespective of the level of the lesion or postinjury duration, perhaps because of weight-bearing during wheelchair use (23, 24), but an effect of neuropathic spondylopathy cannot be excluded (25).

Prevention of bone loss with alendronate was observed at all areas of the hip. These effects were observed as early as 3 months, and by 12 months bone loss was significantly reduced at the total hip, femoral neck, trochanter, and femoral shaft. Furthermore, these effects were sustained for 6 months after cessation of alendronate. In contrast to observations in postmenopausal women (17) and in men (18), BMD did not increase in the hip and spine with alendronate administration. There are several possible reasons for this.

![Fig. 3. Changes in biochemical markers from baseline over 18 months from alendronate or placebo. * P < 0.001.](image-url)
observation. First, once-weekly alendronate may not have been as effective as once-daily. Second, the dose of alendronate in SCI may need to be higher than we used and supple-

Alendronate reduced the parameters of bone resorption in our patients. The rapid decline in βCTX, a marker of bone resorption, from levels 75% higher than normal in the alen-

porosis (17).

have been observed in postmenopausal women with osteo-

this period of drug administration. Furthermore, the initially high urinary calcium excretion rate decreased by 60% to within the normal range by 3 months with alendronate therapy.

No serious adverse events related to alendronate treat-

The rapid decline in βCTX, a marker of bone resorption, from levels 75% higher than normal in the alendronate-treated group was sustained throughout the period of drug administration. Furthermore, the initially high urinary calcium excretion rate decreased by 60% to within the normal range by 3 months with alendronate therapy.

Acknowledgments

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