Randomized Trial of Etidronate Plus Calcium and Vitamin D for Treatment of Low Bone Mineral Density in Crohn's Disease

JESSE S. SIFFLEDEEN,* RICHARD N. FEDORAK,* KERRY SIMINOSKI,† HO JEN,† ERIC VAUDAN,* NEENA ABRAHAM,§ HILLARY STEINHART,‖ and GORDON GREENBERG‖

*Division of Gastroenterology and †Department of Radiology and Diagnostic Imaging, University of Alberta, Edmonton, Alberta, Canada; §Houston Center for Quality of Care and Utilization Studies and Division of Gastroenterology, Michael E. DeBakey Veterans Affairs Medical Center, Baylor College of Medicine, Houston, Texas; and ‖Division of Gastroenterology, University of Toronto, Toronto, Ontario, Canada

Background & Aims: **Crohn's disease causes an increase in osteopenia and osteoporosis. This study assessed the efficacy of adding etidronate to calcium and vitamin D supplementation for treatment of low bone mineral density in Crohn's disease.** ***Methods:*** **One hundred fifty-four patients with Crohn's disease with decreased bone mineral density, determined by using dual-energy x-ray absorptiometry, were randomly assigned to receive etidronate (400 mg orally) or not for 14 days; both groups were then given daily calcium (500 mg) and vitamin D (400 IU) supplementation for 76 days. This cycle was repeated 8 times during a period of 24 months. Biochemical characteristics and bone mineral densities were assessed at 6, 12, and 24 months.** ***Results:*** **After 24 months bone mineral density significantly increased from baseline in both the etidronate- and the non-etidronate–treated groups (both groups receiving calcium and vitamin D supplementation) at the lumbar spine ($P < .001$), ultradistal radius ($P < .001$), and trochanter ($P = .004$) sites, but not at the total hip. The increase in bone mineral density was similar in each treatment group. No bone mineral density differences were found when groups were analyzed according to gender, corticosteroid use, bone mineral density at baseline, or age.** ***Conclusions:*** **Low bone mineral density is frequently associated with Crohn's disease. Supplementation with daily calcium and vitamin D is associated with increases in bone mineral density. The addition of oral etidronate does not further enhance bone mineral density.**

Osteopenia and osteoporosis are well-described complications of CD, with reported frequencies of 36%–55% and 6%–58%, respectively.[1–11] The pathogenesis of the bone loss associated with this condition is not completely understood, but studies suggest that corticosteroid use, poor nutrition, disease activity, calcium and vitamin D deficiencies, proinflammatory cytokine action on osteoclast and osteoblast activity, and sex hormone deficiencies might be involved.[1,2,4,6,9–18] Many studies have reported an association between markers of bone resorption and low bone mineral densities (BMDs) in the case of these patients with CD, findings that suggest enhanced osteoclast activity.[8,10,19–22] The lowered BMDs of patients with CD have further been associated with increased incidences of fractures in several studies.[23–25]

Prevention and treatment of the low BMD associated with CD include education, lifestyle changes (regular exercise, smoking cessation), vitamin D and calcium supplementation, and bisphosphonate therapy. The daily calcium dose necessary to prevent a negative calcium balance is 1000 mg/day of elemental calcium for men and premenopausal women and 1200–1500 mg/day for women and men older than age 50 years. The recommended daily intake of vitamin D is 400–800 IU for individuals with normal vitamin D serum levels.

One 12-month study of 17 corticosteroid-treated male and female patients with IBD showed calcium (1000 mg/day) and vitamin D (250 IU/day) supplementation to have no effect on BMD; however, the base diet of these patients contained considerably less than the recommended daily intakes of dietary calcium and vitamin D.[26] In another randomized, placebo-controlled study of 75 women and men with CD, a supplement of vitamin D (1000 IU/day) prevented bone loss in the forearm over 12 months.[12] However, the basal dietary intake of vitamin D in this group of patients was also low, only 20% of the daily recommended amount.[27] A randomized, controlled study of 33 patients with CD who received supplemental calcium (1000 mg/day) plus vitamin D (1000 IU/day), with or without sodium fluoride 75 mg/day, found that calcium and vitamin D had no impact on BMD during a period of 12 months, whereas the addition of fluoride resulted in a significant increase in BMD.[28] In another randomized study of 117 patients with CD, low impact aerobic exercise was not found to lead to an increase in spinal BMD after 12 months. Nevertheless, subgroup analysis did demonstrate that increases in BMD were associated with the number of exercise sessions completed.[29,30] Recently, a placebo-controlled trial involv-

Abbreviations used in this paper: BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; NTx, N-telopeptide.

1542-3565/05/$30.00
PII: 10.1053/S1542-3565(04)00663-9

ing 32 patients with osteopenia and CD demonstrated that alendronate (10 mg/day) increased BMD by 3%–5% during a period of 1 year.[31]

The primary mode of bisphosphonate action involves inhibition of osteoclast activity and induction of osteoclast apoptosis.[32,33] Etidronate, a first-generation bisphosphonate, has been shown to improve BMD at the lumbar spine for postmenopausal women and for patients on corticosteroid therapy (mean increases of 1.7%–5.7% above baseline after 2 years) with a cyclical regimen (etidronate [400 mg/day] for 14 days, followed by supplemental calcium [500 mg/day] for 76 days).[34–43] Effects on hip BMD have been less consistent.[37,39,43] There are no studies of cyclical etidronate treatment for those with CD. The aim of the current study was to assess the efficacy of 2 years of calcium and vitamin D supplementation, either with or with out cyclical etidronate therapy, on the BMDs of patients with CD.

Materials and Methods

Study Participants

Two hundred twenty-four consecutively encountered patients who had either active or quiescent CD and who were attending the Inflammatory Bowel Disease Referral Clinic at the University of Alberta Hospital (Edmonton, Alberta, Canada) and 18 patients from Mount Sinai Hospital (Toronto, Ontario, Canada) were identified as possible experiment participants between September 2000 and July 2001. They completed a questionnaire documenting age, CD diagnosis date, gender, smoking status, and number of flare-ups requiring a visit to the physician and/or corticosteroid use in the preceding year. After a baseline BMD, patients were classified into 3 groups: normal bone density ($T \geq -1.0$) (not included in the current study), osteopenia (T between -1.0 and -2.5), and osteoporosis ($T < -2.5$) (included in the current study).[44]

Treatment and Randomization

At baseline, 70/224 patients (36%) had normal BMD. Patients with normal BMD were subsequently followed by their respective physicians with standard of care and were not randomized or included in this study. The remaining154/224 patients (64%) had decreased BMDs; 31 of this latter group (13%) had osteoporosis, and 123 (51%) had osteopenia. This group of 154 patients formed the cohort for this study. The following exclusion criteria were applied at baseline to those with low BMD: age < 18 years; bone disorders other than osteoporosis; abnormal thyroid function; serum creatinine $\geq 2\times$ normal; clinical short bowel syndrome; ongoing parenteral or enteral nutrition therapy; spinal anatomy distortions that would not allow adequate assessment of BMD; and treatment with bisphosphonate or fluoride therapy during the 24 months before study entry, or with calcium supplements of more than 1.0 g/day or vitamin D supplements greater than 1000 IU/day during the 6 months before study entry. Postmenopausal women were not excluded from the study. Women on oral contraceptives or hormone replacement therapy were also not excluded, as long as the therapy had been implemented at least 3 months before starting the study and was continued throughout the study period.

These 154 patients with decreased BMDs met inclusion criteria and were randomly assigned to 1 of 2 groups. The etidronate treatment group received etidronate (400 mg orally) for 14 days and then took supplemental calcium carbonate (500 mg) plus vitamin D (400 IU) for the next 76 days. The non-etidronate treatment group received no treatment for the first 14 days and then took supplemental calcium carbonate (500 mg) and vitamin D (400 IU) for the next 76 days. This cycle was repeated 8 times during a period of 24 months by both groups. Patients were instructed to take the study drug (etidronate) at least 30 minutes before breakfast with a large glass of water. Estimations of dietary calcium intake were based on the patients' habitual intakes of dairy products as assessed by a dietitian. Patients were instructed to take the calcium and vitamin D supplements with the evening meal. Randomization occurred in blocks of 20. Concealment of allocation was assured by the use of a sealed opaque envelope. Study treatment was distributed by a pharmacist independent to the trial.

For the chosen experiment subjects, percent changes in BMD, blood biochemistry, and urine biochemistry were assessed at 6, 12, and 24 months. At each visit, a history of adverse events was obtained, and patients completed a questionnaire documenting smoking status, number of flare-ups requiring a visit to the physician, and/or corticosteroid use during the preceding year. Any deviations from the protocol were recorded.

Objective

The primary outcome measure was the difference between groups in the percent change in BMDs at 24 months. The secondary outcome measure was the difference between baseline and 24 months in the percent change in BMDs. Additional analysis of BMD results was carried out on the basis of gender, corticosteroid use, age, and baseline BMD. Post hoc exploratory analysis divided patients into osteopenic and osteoporotic subgroups and then examined the proportion of patients who had change in BMD according to treatment assignment.

Compliance

At each visit, participants were supplied with the study medications they needed to take until the next follow-up visit. Any tablets not used had to be returned. Compliance, expressed as the percentage of required intake, was calculated at the end of the trial by using these tablet counts.

Bone Mineral Density Measurements

BMDs (g/cm^2) of the lumbar spine (L1–L4), the left total hip and trochanteric region, and the right ultradistal radius were determined by dual-energy x-ray absorptiometry (DXA) (Hologic