

## Alendronate and male osteoporosis

Abdullah Alkhenizan, MD, CCFP Saleh Almarri, MD, ABFM Michael F. Evans, MD, CCFP

**Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J, et al. Alendronate for the treatment of osteoporosis in men. *N Engl J Med* 2000;343:604-10.**

### Research question

Does alendronate treatment prevent or reverse bone loss in men with osteoporosis?

### Type of article and design

Randomized controlled trial of therapy.

### Relevance to family physicians

Osteoporosis in men has been relatively neglected as a subject of studies in the medical literature. Although osteoporosis is generally regarded as a women's disease, up to 30% of hip fractures and 20% of vertebral fractures occur in men.<sup>1,2</sup> Lifetime risk, from the age of 50 years, of sustaining an osteoporotic fracture of the hip, spine, or wrist is about 5% for men and 15% for women, and up to 17% of men could experience a hip fracture by the age of 90.<sup>3</sup> Several risk factors for osteoporosis in men have been described, including low body mass index, smoking, high alcohol consumption, corticosteroid therapy, physical inactivity, hypogonadism, transplantation, and thyroid and parathyroid disorders.<sup>4,5</sup> As the population ages, osteoporosis in men could become a more frequent concern. This is the first large randomized controlled trial of treatment of osteoporosis in men. Our obvious question is: Does therapy make a difference?

### Overview of study and outcomes

In this international trial, 241 men (aged 31 to 87; mean age 63) were assigned in a ratio of 3:2 to receive 10 mg of alendronate or placebo daily for up to 2 years in a double-blind manner. Chief entry criteria were a bone mineral density (BMD) at the femoral neck at least 2 standard deviations (SD), and a BMD at the lumbar spine at least 1 SD, below the mean value in normal young men, or a BMD at

the femoral neck at least 1 SD below the mean in normal young men and at least one vertebral deformity or a history of osteoporotic fracture. Men were identified primarily at osteoporosis clinics or during community assessments of BMD. Men with secondary causes of osteoporosis, other than low serum free testosterone concentrations, were ineligible. This included those taking medications, those with medical conditions associated with bone loss, and those with other bone diseases, renal disease (indicated by a serum creatinine concentration >144 µmol/L), severe cardiac disease, history of cancer, recent history (within the previous year) of peptic ulcer or esophageal disease, or esophageal abnormalities that delayed esophageal emptying.

Ten men (seven in the placebo group and three in the alendronate group) receiving stable doses of testosterone were included in the study. All the men were given calcium (500 mg daily in the form of calcium carbonate) and vitamin D (400 IU daily in the United States and 400 to 450 IU daily in other countries) supplements. Primary end point of the study was the BMD of the lumbar spine.

### Results

Baseline characteristics of the 146 men in the alendronate group and the 95 men in the placebo group were similar. Mean BMDs at lumbar spine, femoral neck, and hip were approximately 2.0, 2.2, and 2.1 SD below the respective mean values for young men. About 50% of the men had vertebral fractures at baseline, and 29% had multiple vertebral fractures. Eighty-three percent of the men in the placebo group and 86% of the men in the alendronate group completed the study. Five patients (2%) were lost to follow up.

Percentage changes in BMD from baseline, for placebo and alendronate groups, respectively, for the following areas were: lumbar spine 1.8% and 7.1%, femoral neck -0.1% and 2.5%, trochanter 1.3% and 4.3%, hip 0.6% and 3.1%, and total body 0.4% and 2.0%. A significant absolute difference between the two groups appeared in all areas.

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**Dr Alkhenizan** is a Clinical Fellow in the care for the elderly fellowship and a Fellow in the Clinical Epidemiology program at the University of Toronto. **Dr Almarri** is a Clinical Fellow in the care for the elderly fellowship in the Department of Family and Community Medicine at the University of Toronto. **Dr Evans** teaches in the Department of Family and Community Medicine at the Toronto Western Hospital, University Health Network, at the University of Toronto.

The proportion of men whose height decreased by at least 10 mm over the 2-year period was 13% in the placebo group and 3% in the alendronate group.

Blinded review of x-ray films revealed that the incidence of vertebral fractures was 7.1% in the placebo group and 0.8% in the alendronate group ( $P=.02$ ). Three men in the placebo group and one man in the alendronate group had painful vertebral fractures; incidence of nonvertebral fractures in the two groups (five in the placebo group and six in the alendronate group) was similar. Fourteen men withdrew from the study because of adverse effects: 10 (11%) in the placebo group and four (3%) in the alendronate group ( $P=.02$ ). There were no significant differences between groups in incidence of serious adverse effects, drug-related adverse effects, drug-related withdrawals from therapy, or laboratory test abnormalities.

### Analysis of methodology

This was a well-designed study with excellent follow up (98%). Analysis was based on the intention-to-treat principle. The primary end point of changes in the BMD of lumbar spines was statistically significant in the alendronate group. Most of the men were white (98%). The study was not empowered to detect significant changes in other important clinical outcomes, such as rates of hip fractures.

The primary end point of this study was "disease oriented" rather than "patient oriented" in that the outcome of interest was based on measuring vertebrae on x-ray films for changes (ie, loss of height indicates fracture) or noting changes in BMD. Family physicians would be more interested in outcomes such as reduction in the number of men who come in with hip fractures. Having said this, evidence from observational studies shows that risk of hip fracture increased 2.6-fold for each SD reduction in BMD at the femoral neck, and risk of spine fractures increased 2.3-fold for each SD reduction in BMD at the spine.<sup>6</sup>

### Application to clinical practice

Results of this study show us that the reduction in incidence of vertebral fractures, increase in BMD, and maintenance of height in men taking alendronate are consistent with the effects of alendronate in women with osteoporosis. In this study, 16 patients needed to be treated for 2 years to prevent one vertebral fracture. In the Fracture Intervention Trial,<sup>7,8</sup> 59 low-risk and 15 high-risk women needed to be treated for 4.2 and 3 years, respectively, to prevent one vertebral fracture. Unlike in the trials with women, there was no difference in patient-oriented outcomes, such as rates of hip fracture.

### Bottom line

- Family physicians should watch for osteoporosis in men, especially in patients with risk factors, such as low body mass index, smoking, high alcohol consumption,

corticosteroid therapy, physical inactivity, hypogonadism, transplantation, and thyroid and parathyroid disorders.

- In men with osteoporosis, alendronate increased BMD, reduced the rate of vertebral fractures, and prevented decreases in height.
- No reduction was seen, however, in what brings patients to the office, such as painful vertebral fractures or hip fractures.
- Benefits of alendronate therapy for men with osteoporosis were similar to those observed for women with osteoporosis.
- This trial followed 241 men with osteoporosis for 2 years. Further studies with larger numbers are needed to assess the long-term effects of alendronate and its effect on prevention of hip fractures in these men. ❖

### Points saillants

- Les médecins de famille devraient être à l'affût de l'ostéoporose chez les hommes, en particulier chez les patients qui présentent des facteurs de risque comme un indice de masse corporelle faible, le tabagisme, une consommation élevée d'alcool, une thérapie aux corticostéroïdes, l'inactivité physique, l'hypogonadisme, une greffe et des troubles de la thyroïde ou de la parathyroïde.
- Chez les hommes présentant de l'ostéoporose, l'alendronate augmentait la DMO, réduisait le taux de fractures vertébrales et prévenait des réductions de taille verticale.
- Par contre, on n'a observé aucune réduction dans les facteurs amenant les patients à consulter, comme les douloureuses fractures d'une vertèbre ou de la hanche.
- Les bienfaits d'une thérapie à l'alendronate pour les hommes souffrant d'ostéoporose étaient semblables à ceux observés chez les femmes présentant la même affection.
- Cet essai faisait le suivi pendant deux ans de 241 hommes souffrant d'ostéoporose. Il est nécessaire d'effectuer des études plus approfondies sur des sujets plus nombreux pour évaluer les effets à long terme de l'alendronate et ses répercussions sur la prévention des fractures de la hanche chez ces hommes.

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